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Risk factors of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus in Mainland China.

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Running title: Risk factors of DR in China

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Risk factors of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus in Mainland China

Abstract:

Objectives: To explore the risk factors of diabetic retinopathy (DR) and sight threatened diabetic retinopathy (STDR) among Chinese patients with diabetes.

Design, setting and participants: A cross-sectional investigation was performed in eight screening clinics in six provinces across mainland China. Information of risk factors was recorded in screening clinics, and in these risk factors, sex, age, diagnosis age, diabetes duration, SBP, DBP, FBG, HbA1c were recorded in each clinic while others were partially collected. Relationship between risk factors and DR, STDR was explored in both eight factors mentioned above and all factors.

Main outcomes and measures: Risk factors of DR and STDR, and a nomogram of the results.

Results: Younger age, longer diabetes duration, higher SBP, higher FBG, and higher HbA1c were independent risk factors for both DR and STDR in eight-factor analyses. In all-factor analysis, younger age, longer diabetes duration, higher SBP, oral medicine, and insulin use were independent risk factors for both DR and STDR, while higher PBG, HbA1c, triglyceride and LDL were independent risk factors only for DR, and higher FBG only for STDR.

Conclusions: In this cross-sectional investigation, several risk factors were found for DR and STDR. What's worth to mention is that FBG, PBG and HbAc were all risk factors for DR or STDR, which implied that a stricter blood glucose control for clinical

practice was required.

Key words: diabetic retinopathy, risk factor, glucose, WHR, BMI

Strength and limitations of this study

- This is a cross-sectional population-based (13473 subjects) estimate of the risk factors of diabetic retinopathy
- The study was performed in eight hospitals from 6 different provinces in mainland China, and participants were from hospitals and communities which included rural and urban regions.
- We separately analyzed the risk factors for diabetic retinopathy (DR) and sight threatened diabetic retinopathy (STDR), and several differences were found in our study especially in blood glucose and HbA1c.
- Owing to the multi-center design, some information was not comprehensively collected, which resulted in an imperfection in risk factor analysis.

INTRODUCTION:

Diabetes Mellitus (DM) is a metabolic syndrome with an increasing prevalence and high rate of mortality [1]. Diabetic retinopathy (DR) is a common ocular complication of DM, which is considered as a leading cause of vision loss and vision impairment in adults [2]. With the progression of DR, quality of life of patients is getting lower and the financial burden of society is increasing, both in DR screening and therapy [3,4].

DR has been considered to be correlated with many other diabetes-related complications, like nephropathy, peripheral neuropathy, low bone density and cardiovascular events, which impaired the quality of life and showed a high rate of mortality [5-8]. Therefore, early diagnosis and management of DR also indicated a realistic significance.

A great deal of epidemiologic studies of DR, either cross-sectional studies [9-18] or cohort studies [19-28], are conducted worldwide, exploring the risk factors that is associated with the disease and aiming at the prevention and management of disease. Older age, female, duration of diabetes, renal complications of diabetes, poor glycemic control, high lipid levels, hypertension were already reported as risk factors of DR or has an impact on DR progression [9-26], which was often evaluated using Treatment Diabetic Retinopathy Study (ETDRS) classification [27]. Of these reported risk factors, duration of diabetes, hyperglycemia and hypertension were considered as most important risk factors for progression of vision loss [29]. However, DR and risk factors of DR always gained little attention, and the compliance of eye screening is

often unsatisfied [30]. More studies and publicity of risk factors are required.

In China, a few studies are reported and all these population-based studies are conducted in a limited area [21,25,28]. Therefore, a cross-sectional investigation in 6 provinces (both in Northern and Southern area) was conducted, and the prevalence of DR and basic epidemiological characteristics has been reported in former published article [31]. In this study, we aimed to explore the risk factors associated with DR in mainland China.

METHODS:

Research design:

Lifeline Express Diabetic Retinopathy Screening Program was conducted nationwide, which is a cross-sectional investigation in eight hospitals from 6 different provinces (Shandong, Henan, Inner Mongolia, Jilin, Guangxi, Guangdong Provinces). Subjects came from hospitals or local communities (1/3 from hospital patients, 1/3 from city residents, and the other 1/3 from rural residents) between April 2014 and October 2015. The study protocol was approved by the Peking University Third Hospital Ethics Committees and the written informed consent was provided for each subject. The study was performed in accordance with the Declaration of Helsinki.

Subjects in hospital were diagnosed as DM by physicians and transferred to eight screening clinics and subjects from community were recruited by advertisement. Of all the screening clinics, 3 of which were in the south and the other 5 were in the north of

China. All subjects received a digital, colorful and non-stereoscopic retinal photograph, which was taken by a non-mydriatic auto fundus camera. The photograph included 2 fields for each eye: one centered at the optic disc and the other centered at the macula.

DR/STDR diagnosis and grading:

DR was graded by trained and certified optometrists and ophthalmologists in Lifeline Lifeline Express Diabetic Retinopathy Central Assurance Centre. All of the graders underwent periodic tests to ensure the accuracy of grading. DR was graded by fundus photographs of two eyes into no retinopathy (R0) and diabetic retinopathy (other stages), and DR was also graded as none sight-threatening diabetic retinopathy (non-STDR), sight-threatening diabetic retinopathy (STDR) according to the UK guidelines [32]. Non-STDR was recognized as R0 and R1, and STDR was identified as present if any features of maculopathy (M1), pre-proliferative DR (R2) or PDR (R3) were found. If the fundus photographs were unrecognized which means missing or unable to diagnose due to variable reasons in both eyes like cataract and vitreous opacities, the patients were excluded. If photograph of one eye was unrecognized, the final diagnosis was determined by the only remained photograph. If the remained photograph was graded as R0, patients were excluded due to lack of evidence, if graded as R1, patients were diagnosed as DR and excluded for the STDR analysis, if graded as M1, R2 or R3, patients were diagnosed as DR and STDR.

Information collection:

At the time of clinical visit, the following information was recorded including gender, age, diagnosis age, diabetes duration(calculated from age and onset age), diabetes types (evaluated by physicians in screening clinics), body mass index (BMI, calculated from measured height and weight), waist–hip ratio (WHR, calculated from measured waistline and hipline), and types of medication therapy. Systolic blood pressure(SBP), diastolic blood pressure (DBP), fasting blood-glucose (FBG), postprandial blood glucose 2 hours after eating (PBG) and glycosylated hemoglobin(HbA1c) was measured at the screening clinics, and fasting blood samples were collected for cholesterol, triglyceride, high density lipoprotein(HDL), low density lipoprotein(LDL), blood urea nitrogen(BUN), serum creatinine(SCr). Gender, age, diagnosis age, diabetes duration, blood pressure, FBG and HbA1c was screened for each patient, while other information was limited due to environment and devices.

Statistical analysis:

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL) software. The independent t-test was used to compare continuous variables, and the chi-square test was used to compare discontinuous variables among groups. Due to limited numbers of type 1 and gestational diabetic patients, we only analyzed the data of type 2 diabetic patients.

We firstly conducted analysis of relationship between the risk factors and DR, which contains 3 major steps. In the first step, mean values and median values of the main variables were calculated. In the second step, univariate analyses of the associations

between the existence of DR and other risk factors. In this step, several continuous variables, including age, diabetes duration, blood pressure (BP), BMI, WHR were also transferred into categorical variables, to explore detailed relationship with DR. Age was divided into groups with 10-year interval, and diabetes duration with 5-year interval. BP was transferred into normal BP, level 1 hypertension, level 2 hypertension, and severe hypertension [33]. BMI was divided into underweight (<18.5), normal weight (≥18.5 & <24), overweight (≥24 & <27) and obesity (≥27). WHR was divided into normal WHR (male ≤0.90 & female ≤0. 85) and abdominal obesity (male 0.90 & female ≤0. 85), and was also divided into male and female. In the third step, multicollinearity diagnosis was performed and a variance inflation factor (VIF) >10 was thought a high collinearity [34], furthermore, variables with high collinearity were evaluated and variable which was more relevant to the research purpose was remained determined by two researchers (YJR and LY). In the fourth step, binary logistic regression analyses were carried out, taking the existence of DR as the dependent variable and all risk factors, which were significantly associated with the existence of DR in the former step or considered as an important risk factor based on existed studies, as independent variables. Due to limitations of information collection, we separately analyzed the eight risk factors which was completely collected in each screening clinics (eight-factor analysis), and all risk factors (all-factor analysis), furthermore, difference between two analyses was discussed.

Then, relationship between the risk factors and STDR was also conducted in previous way. Odds ratios (ORs) and 95% confidence intervals were presented. An α level of

0.05 was adopted as the significance level.

At last, nomograms for DR and STDR risk factors were developed, and risk factors that showed significant difference in former binary logistic regression were treated as predictors. Interpretation of the nomogram in prediction of DR has been reported in former studies [35], and using each score of predictors, risk incidence of DR and STDR would be calculated.

Results:

From April 2014 to October 2015, 13473 DM patients from 6 provinces were enrolled in the study. 45.9% patients were from southern provinces (6180/13473) and 54.1% from northern provinces (7293/13473). Of all the patients, 13304 patients were type 2 diabetes, 96 were type 1 diabetes, and 73 were gestational diabetes. Patients were divided into no DR and DR, non-STDR and STDR, according to the fundus photographs grading. 571 patients were excluded from DR risk factor analysis, and 683 patients were excluded from STDR risk factor analysis due to diagnostic rules mentioned above, and finally 12733 patients were included in DR risk factor analysis and 12621 patients were included in STDR risk factor analysis (shown in Figure 1).

Firstly, analyses of DR risk factors were performed, and basic characteristics of all risk factors were shown in Table 1. The result of univariate analyses indicated that age, diagnosis age, diabetes duration, SBP, DBP, waistline, hipline, WHR, medicine (oral and insulin), FBG, PBG, HbA1c, BUN, and LDL was statistically significantly different between groups ($p<0.05$), and no significant difference was found in gender, BMI, Cr, cholesterol, triglyceride, and HDL ($p>0.05$).

Furthermore, categorical analyses showed that patients were getting less likely to suffer from DR per 10 years after 60 years old, while no difference was found before 60. Incidence of DR increased significantly per 5-year diabetes duration, while it stopped increasing after 20 years of diabetes duration. Results of blood pressure indicated that incidence increased with the rise of level, and when it came to level 3 BP, it didn't differ from level 2. Female had a higher WHR in DR while male didn't, and whether in a condition of abdominal obesity didn't influence the incidence of DR.

Then, multivariate analyses were performed. Multicollinearity diagnosis was performed in both eight-factor analysis and all-factor analysis. The results excluded diagnosis age (highly correlated to age and DR duration) in eight-factor analysis, and excluded diagnosis age (highly correlated to age and DR duration), waistline, hipline (both of which highly correlated to WHR) in all-factor analysis due to the high collinearity. Multiple logistic regression analyses were carried out and the results were shown in Table 3. Results of eight-factor analysis (with diagnosis age excluded) showed that younger age, longer diabetes duration, higher SBP, higher FBG, and higher HbA1c was the independent risk factor for DR ($p<0.05$), and sex, DBP was not significantly associated with DR ($p>0.05$). Multiple logistic regression of all-factor analysis (with diagnosis age, waistline, hipline excluded) was also conducted and the result showed that younger age, longer diabetes duration, higher SBP, HbA1c, PBG, oral medicine, insulin use, higher triglyceride, and higher LDL were the independent risk factors for DR ($p<0.05$), while sex, DBP, BMI, FBG, WHR, BUN, Cr, cholesterol, and HDL were not associated with DR ($p>0.05$).

After DR risk factors analyses, analyses of STDR risk factors were conducted, and characteristics of risk factors were shown in Table 2. Age, diagnosis age, diabetes duration, SBP, DBP, HbA1c, FBG, PBG, waistline, WHR, medicine, Cr, LDL showed statistically significant difference between groups ($p<0.05$), while gender, BMI, hipline, BUN, cholesterol, triglyceride, HDL was not significantly different. After multicollinearity diagnosis, diagnosis age was dropped in eight-factor analysis and diagnosis age, waistline and hipline were dropped in all-factor analysis. Result of multiple logistic regression was shown in Table 3. Results of eight-factor analysis (with diagnosis age dropped) showed that younger age, longer diabetes duration, higher SBP, DBP, FBG, and HbA1c were the independent risk factor for STDR ($p<0.05$), and sex was not significantly associated with STDR ($p>0.05$). Results of all-factor analysis indicated that younger age, longer diabetes duration, higher SBP, higher FBG, oral medicine and insulin use were regarded as independent risk factors for STDR ($p<0.05$) while other risk factors showed no significant difference ($p>0.05$).

Finally, we developed a nomogram to simplify the presentation and understanding of our results (Figure 2).

Discussion:

According to the result of our study, we tried to find a reasonable explanation and an internal relationship between DR, STDR and risk factors.

Firstly, focusing on univariate analysis, 14 out of 20 risk factors were observed significantly different between no DR and DR, and 13 out of 20 factors between non-STDR and STDR. Basically, all risk factors were divided into incontrollable and

controllable risk factors.

Incontrollable factors included gender, age, diagnosis age, and diabetes duration. In both no DR/ DR and non-STDR/STDR analysis, gender showed no difference, which was also reported in several previous studies [10, 12], while results of some studies were controversial [11,13]. Significantly younger age was observed in DR and STDR, and longer duration of diabetes was also found in DR and STDR. Longer duration may represent a longer time of retinal toxicity to retina induced by high glucose, which was thought to be associated with both vascular and neural death in retina [36]. Existed studies showed an older or extreme younger age in DR patients than no DR patients [26], while older age was thought as a protective variable for DR/STDR in our study, especially in DM patients older than 60. We thought that the possible reason of this phenomenon was that younger age of DM diagnosis played an important role in DR and STDR progression, which may be explained by genetic differences [18]. Furthermore, we explored the relationship between age and HbA1c, diabetes duration, medicine, the results indicated that with age increasing, diabetes duration increased, while HbA1c and use of insulin decreased, which implied that although the duration of diabetes increased, older people had a better glucose management and required milder medicine. In this way, age was analyzed as a protective factor.

Controllable risk factors included types of variables as following: index of obesity, blood pressure, medicine, blood glucose, renal function and blood lipid. Both DR and STDR showed a significantly higher WHR, blood pressure, blood glucose, LDL and a higher incidence of insulin use than no DR and non-STDR, and BUN was only

significantly higher in DR than no DR, while Cr was only significantly higher in STDR than non-STDR. WHR was thought to be associated with DM [37], and was also thought as a risk factor for severe DR in women [38], and our study showed similar results in univariate analysis. High blood pressure indicated a significantly higher incidence of DR and STDR, while the effect didn't increase after a certain level. Blood glucose and LDL were significantly higher in DR and STDR group than no DR and non-STDR group, while cholesterol level showed no significant difference, which indicated DR and STDR group had a bad management of blood glucose and LDL. BUN and Cr were both common variables that reflected renal function, and our study indicated that DR and STDR showed a higher level of renal injury than no DR and non-STDR. Application of oral medicine and insulin was also reported as risk factors in former studies, which may be owing to the severity of disease condition [11].

Secondly, the results of multiple logistic regression analyses showed independent risk factors of DR and STDR were similar in eight-factor analysis (with diagnosis age dropped) and were kind of different in all-factor analysis (with diagnosis age, waistline, hipline dropped). In all-factor analysis, age, diabetes duration and SBP were independent risk factors for both DR and STDR, while PBG, HbA1c, Triglyceride and LDL were independent risk factors only for DR, and FBG only for STDR. Age, diabetes duration and SBP has been reported as independent risk factors for DR or DR progression [10,20,25], while differences on blood glucose were hard to explain. HbA1c has been reported to be an independent risk factor in development and progression of DR in former studies [18,21], while there existed little evidence on PBG in

DR progression. HbA1c was long considered to represent the management condition of blood glucose, and bad glucose management contributed to the occurrence and progression of DR [9,10,11]. PBG was reported to be abnormal in 31% DM patients whose FBG was normal [39], so it was considered an important diagnostic factor for DM. PBG was more valuable in prediction of ischemic and hemorrhagic stroke, cardiovascular disease mortality, while FBG was weak in prediction [40,41], therefore, we thought that PBG was a risk factor for severe complications of DM, such as DR. Possible mechanism of PBG in progression of DR is PBG reflected capacity of insulin secretion, the peak of which was shown to be delayed in type 2 DM [42], and high level of PBG indicated that insulin secretion was relatively insufficient which may result in a blood glucose fluctuation after food intake, and did more harm to targeted organs. Our study firstly found that FBG was an independent risk factor for STDR, meanwhile we also admit that OR was only 1.043 for 1 unit increase in FBG, which had limited meaning in predicting incidence of STDR, which was also indicated in nomogram. No existed studies showed that FBG was an independent risk factor for DR, which may be caused by a higher predictive value of HbA1c in these studies, and possible mechanism of FBG for STDR required further studies. LDL and triglyceride were also independent risk factors for DR, which indicated that management of blood lipids were very important for occurrence of DR, while it had limited meanings for STDR compared with other risk factors.

Our study also had some limitations. Firstly, due to limitations of device and screening environment, several variables were incomplete and if we meant to analyze all

variables in this study, lots of data would be abandoned, and the result of multivariate regression may be influenced. Secondly, although we tried to balance the resources of patients, from north and south, from urban and rural areas, patients enrolled in final all-factor logistic regression were not fully balanced due to the exclusion of missing data. Thirdly, patients and screening clinics were not stratified sampled, and couldn't fully represent the patient in mainland China. Fourthly, our study design was cross-sectional, compared to cohort studies, cross-sectional studies had weaker strength of evidence, and the results should be carefully explained. More cohort studies focusing on several areas of China was required.

Conclusions:

Our study demonstrated that age, diabetes duration and SBP were independent risk factors for both DR and STDR. PBG, HbA1c, Triglyceride and LDL were independent risk factors only for DR, and FBG only for STDR. This result was similar to existed studies and may provide some evidence on clinical prevention of DR and STDR, especially we firstly brought up that FBG, PBG, HbA1c were all important predictors for occurrence or progression of DR, and this required a stricter glucose control. More DR screening and information collection were required, which may decrease the incidence of DR and improved clinical results.

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Author Contributions: Y.L. and J.Y designed the whole study, completed the data collection, and wrote the manuscript. J.Y and L.T performed the data analysis and L.T contributed to the writing of the manuscript on epidemic part. H.L. and X.J. contributed to the study design, and contributed to the writing of the manuscript. M.Z. assisted with the study design, data collection and contributed to the editing of the manuscript. X.L. oversaw the study, gave advise on study design, and revised the manuscript. X.L. is the guarantor of this study and had full access to all the data in this study, and X.L. also takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figures.

Figure 1 Flow diagram of the data processing.

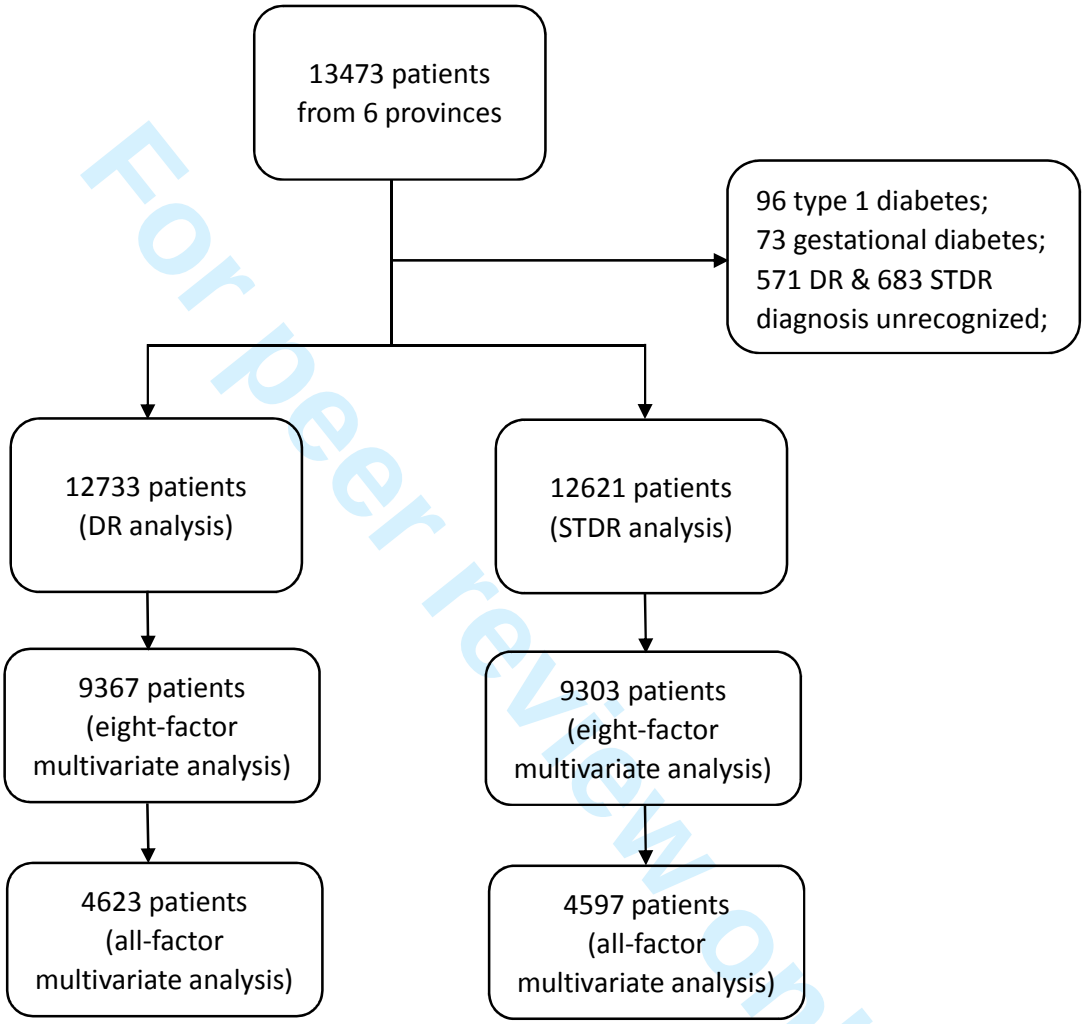

Figure 2 Nomograms for DR (A) and STDR (B) risk factors. Risk factors were chosen based on results of logistic regression analysis. Each risk factor of the patient was assessed on basis of the nomogram and got a point. Aggregated points of each point corresponded to a particular occurrence probability of DR or STDR.

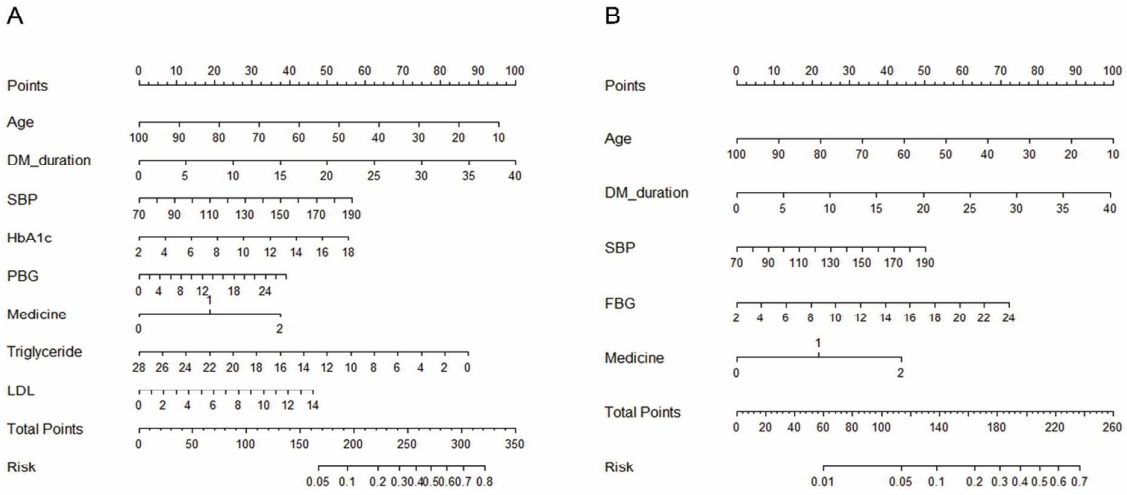

Table 1—Univariate analysis of DR risk factors. (N=12733)

Variable	n	No DR (n=8772)	n	DR (n=3961)	P	OR	95%CI
Male gender, n(%)	8772	3985 (45.4%)	3961	1851 (46.7%)	0.172		
Age, years (SD)	8770	63.0(10.3)	3959	61.0 (9.8)	**<0.001**		
<30, %	11	30.6%	25	69.4%			
30-40, % (vs.<30)	143	66.8%	71	33.2%	0.757	1.128	0.526-2.423
40-50, % (vs.30-40)	733	64.2%	408	35.8%	0.469	1.121	0.823-1.527
50-60, % (vs.40-50)	2138	63.2%	1243	36.8%	0.542	1.004	0.908-1.201
60-70, % (vs.50-60)	3443	69.7%	1494	30.3%	**<0.001**	0.746	0.680-0.819
>70, % (vs.60-70)	2217	76.0%	700	24.0%	**<0.001**	0.728	0.655-0.808
Diagnosis age, years (SD)	8770	56.3 (10.2)	3959	50.8 (10.3)	**<0.001**		
Diabetes duration, years (SD)	8772	6.7 (5.9)	3961	10.2 (6.8)	**<0.001**		
<5, %	4692	80.0%	1174	20.0%			
5-10, % (vs. <5)	2314	65.7%	1208	34.3%	**<0.001**	2.086	1.898-2.293
10-15, % (vs. 5-10)	1032	57.6%	761	42.4%	**<0.001**	1.413	1.257-1.587
15-20, % (vs. 10-15)	521	48.2%	560	51.8%	**<0.001**	1.458	1.252-1.696
>20, % (vs. 15-20)	213	45.2%	258	54.8%	0.281	1.127	0.907-1.400
BMI (SD)	6000	24.7 (3.5)	2854	24.9 (3.9)	0.116		
Underweight, %	97		53				
Normal weight, % (vs. underweight)	3348		1543		0.326	0.843	0.600-1.185
Overweight, % (vs. normal weight)	2175		1043		0.414	1.041	0.946-1.145
Obese, % (vs. overweight)	380		215		0.076	1.180	0.983-1.417
SBP, mmHg (SD)	8762	133.3 (16.5)	3952	137.0(17.9)	**<0.001**		
DBP, mmHg (SD)	8762	79.6 (9.9)	3952	80.8 (10.8)	**<0.001**		
Normal BP, %	5084	72.3%	1950	27.7%			
BP level 1, % (vs. normal)	2840	66.7%	1420	33.3%	**<0.001**	1.303	1.200-1.414
BP level 2, % (vs. level 1)	665	59.3%	456	40.7%	**<0.001**	1.371	1.198-1.569
BP level 3, % (vs. level 2)	173	57.9%	126	42.1%	0.648	1.062	0.820-1.376
Waistline, cm (SD)	5719	89.3 (10.1)	2735	90.3 (10.6)	**<0.001**		
Hipline, cm (SD)	5719	96.6 (9.7)	2735	97.1 (9.5)	**0.028**		
WHR (SD)	5719	0.926 (0.074)	2735	0.930 (0.069)	**0.007**		
Abdominal obesity, n(%)		4677 (81.8%)		2267 (82.9%)	0.213	1.079	0.957-1.217
Female (SD)	3152	0.915 (0.076)	1501	0.923 (0.072)	**0.002**		
Male (SD)	2567	0.94 (0.070)	1234	0.94 (0.064)	0.674		

Medicine	5793		2797		**<0.001**		
No medicine, %	660	87.0%	99	13.0%			
Oral medicine, % (vs. no medicine)	3296	73.2%	1208	26.8%	**<0.001**	5.407	4.331-6.752
Insulin, % (vs. oral medicine)	1837	55.2%	1490	44.8%	**<0.001**	2.213	2.013-2.434
FBG, mmol/L (SD)	7547	7.8 (2.4)	3517	8.7 (3.0)	**<0.001**		
PBG, mmol/L (SD)	4780	10.7 (3.3)	2095	11.8 (3.5)	**<0.001**		
HbA1c, % (SD)	7762	7.16 (1.65)	3146	7.82 (1.90)	**<0.001**		
BUN, mmol/L (SD)	6357	5.79 (8.19)	2633	6.33 (10.51)	**0.01**		
Cr, μmol/L (SD)	6320	76.5 (112.7)	2615	78.8 (39.2)	0.328		
Cholesterol, mmol/L (SD)	6418	5.04 (2.69)	2651	5.06 (1.31)	0.752		
Triglyceride, mmol/L (SD)	6382	1.87 (1.22)	2635	1.89 (1.26)	0.456		
HDL, mmol/L (SD)	6392	1.37 (0.56)	2642	1.38 (0.57)	0.481		
LDL, mmol/L (SD)	6399	2.72 (1.00)	2643	2.83 (1.00)	**<0.001**		

Continuous variables were reported as mean value and standard deviation, and categorical variables were reported as percentage, OR and 95% CI. P<0.05 was considered statistically significant and marked in bold. n, number; OR, odd ratio; 95%CI, 95% confidence interval; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist hip ratio; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; Cr, creatinine; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2—Univariate analysis of STDR risk factors. (N=12621)

Variable	n	None-STDR (n=10875)	n	STDR (n=1746)	P	OR	95%CI
Male gender, n(%)	10875	4985 (45.8%)	1746	799 (45.8%)	0.952		
Age, years (SD)	10873	62.7 (10.2)	1745	60.4 (9.7)	**<0.001**		
<30, %	32		4				
30-40, % (vs.<30)	181		32		0.757	1.128	0.526-2.423
40-50, % (vs.30-40)	927		205		0.469	1.121	0.823-1.527
50-60, % (vs.40-50)	2785		576		0.542	1.004	0.908-1.201
60-70, % (vs.50-60)	4253		643		**<0.001**	0.746	0.680-0.819
>70, % (vs.60-70)	2160		270		**<0.001**	0.728	0.655-0.808
Diagnosis age, years (SD)	10873	55.4 (10.4)	1745	49.4 (10.4)	**<0.001**		
Diabetes duration, years (SD)	10875	7.2 (6.2)	1746	11.0 (6.8)	**<0.001**		
<5, %	4692		1174				
5-10, % (vs. <5)	2314		1208		**<0.001**	2.086	1.898-2.293
10-15, % (vs. 5-10)	1032		761		**<0.001**	1.413	1.257-1.587
15-20, % (vs. 10-15)	521		560		**<0.001**	1.458	1.252-1.696
>20, % (vs. 15-20)	213		258		0.281	1.127	0.907-1.400
BMI (SD)	7518	24.8 (3.6)	1256	24.8 (3.9)	0.738		
Underweight	120		28				
Normal weight, % (vs. underweight)	4145		703		0.134	0.727	0.478-1.105
Overweight, % (vs. normal weight)	2759		428		0.177	0.915	0.804-1.041
Obese, % (vs. overweight)	494		97		0.054	1.266	0.995-1.610
SBP, mmHg (SD)	10863	133.8 (16.7)	1741	138.1 (18.7)	**<0.001**		
DBP, mmHg (SD)	10863	79.8 (10.0)	1741	81.0 (11.4)	**<0.001**		
Normal BP, %	6164	88.2%	826	11.8%			
BP level 1, % (vs. normal BP)	3584	85.0%	630	15.0%	**<0.001**	1.312	1.173-1.467
BP level 2, % (vs. BP level 1)	892	80.5%	216	19.5%	**<0.001**	1.378	1.161-1.635
BP level 3, % (vs. BP level 2)	223	76.4%	69	23.6%	0.118	1.278	0.939-1.739
Waistline, cm(SD)	7176	89.4 (10.1)	1200	90.7 (10.8)	**<0.001**		
Hipline, cm(SD)	7176	96.7 (9.6)	1200	97.2 (10.1)	0.120		
WHR (SD)	7176	0.926 (0.073)	1200	0.934(0.071)	**0.001**		
Abdominal obesity,n(%)		5872(81.8%)		1004(83.7%)	0.124	1.113	0.970-1.276
Female (SD)	3947	0.92 (0.075)	666	0.93 (0.074)	**<0.001**		

Male (SD)	3229	0.94 (0.069)	534	0.94 (0.065)	0.634		
Medicine	7304		1218		**<0.001**		
No medicine, %	727	93.7%	49	6.3%			
Oral medicine, % (vs. no medicine)	4008	89.6%	465	10.4%	**<0.001**	2.908	1.982-4.267
Insulin, % (vs. oral medicine)	2569	78.0%	724	22.0%	**<0.001**	2.429	2.140-2.757
FBG, mmol/L (SD)	9451	8.0 (2.5)	1521	8.9 (3.1)	**<0.001**		
PBG, mmol/L (SD)	5964	10.9 (3.3)	886	11.9 (3.6)	**<0.001**		
HbAlc, % (SD)	9548	7.25 (1.70)	1280	8.05 (1.97)	**<0.001**		
BUN, mmol/L (SD)	7855	5.89 (9.38)	1072	6.38 (4.99)	0.092		
Cr, μmol/L (SD)	7812	76.2 (102.1)	1060	84.2 (52.3)	**0.012**		
Cholesterol, mmol/L (SD)	7927	5.05 (2.48)	1079	5.06 (1.29)	0.904		
Triglyceride, mmol/L (SD)	7884	1.87 (1.22)	1072	1.94 (1.29)	0.072		
HDL, mmol/L (SD)	7897	1.37 (0.56)	1074	1.38 (0.54)	0.755		
LDL, mmol/L (SD)	7907	2.74 (0.99)	1072	2.82 (1.06)	**0.015**		

Table 3 —Logistic regression of DR and STDR risk factors. (Both in eight-factor analysis and all-factor analysis.)

Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
	DR risk factors analysis						DR risk factors analysis					
	eight-factor analysis (N=9367)			all-factor analysis (N=4623)			eight-factor analysis (N=9303)			all-factor analysis (N=4597)		
Sex (women vs men)	1.026	0.932-1.130	0.169	1.052	0.913-1.213	0.489	0.979	0.855-1.120	0.753	1.176	0.960-1.442	0.118
Age	0.966	0.961-0.971	**<0.001**	0.968	0.961-0.976	**<0.001**	0.961	0.954-0.968	**<0.001**	0.961	0.950-0.972	**<0.001**
Diabetes duration	1.102	1.093-1.111	**<0.001**	1.071	1.059-1.084	**<0.001**	1.102	1.091-1.113	**<0.001**	1.077	1.061-1.094	**<0.001**
SBP	1.015	1.011-1.018	**<0.001**	1.016	1.010-1.021	**<0.001**	1.017	1.011-1.021	**<0.001**	1.017	1.010-1.024	**<0.001**
DBP	0.995	0.989-1.001	0.083	0.994	0.986-1.002	0.152	0.987	0.980-0.995	**0.002**	0.990	0.979-1.002	0.095
FBG	1.040	1.019-1.062	**<0.001**	1.008	0.972-1.046	0.666	1.043	1.016-1.071	**0.002**	1.076	1.028-1.127	**0.002**
HbA1c	1.164	1.128-1.201	**<0.001**	1.102	1.051-1.156	**<0.001**	1.168	1.172-1.250	**<0.001**	1.060	0.994-1.130	0.077
PBG				1.039	1.014-1.065	**0.003**				1.013	0.979-1.048	0.473
BMI				0.991	0.972-1.012	0.406				0.976	0.948-1.005	0.109
WHR				1.527	0.591-3.947	0.382				3.314	0.927-11.842	0.065
Medicine												
Oral vs. no medicine				2.158	1.517-3.069	**<0.001**				3.737	1.721-8.113	**0.001**
Insulin vs. no medicine				3.535	2.455-5.089	**<0.001**				6.856	3.141-14.966	**<0.001**
BUN				1.004	0.997-1.011	0.238				1.002	0.994-1.010	0.598
Cr				1.000	1.000-1.001	0.745				1.000	1.000-1.001	0.121
Cholesterol				0.999	0.955-1.044	0.948				0.995	0.924-1.071	0.890
Triglyceride				0.924	0.873-0.979	**0.007**				0.950	0.878-1.028	0.200

HDL	1.030	0.901-1.176	0.668	0.970	0.789-1.193	0.776
LDL	1.099	1.017-1.187	**0.017**	1.093	0.978-1.221	0.118

P<0.05 was considered statistically significant and marked in bold.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	25-26
		(b) Indicate number of participants with missing data for each variable of interest	25-26
Outcome data	15*	Report numbers of outcome events or summary measures	25-26
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25-26
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risk Factors of Diabetic Retinopathy and Sight Threatened Diabetic Retinopathy: A Cross-sectional Study in 13473 Patients with Type 2 Diabetes Mellitus in Mainland China.

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Title: Risk Factors of Diabetic Retinopathy and Sight Threatened Diabetic Retinopathy: A Cross-sectional Study in 13473 Patients with Type 2 Diabetes Mellitus in Mainland China.

Running title: Risk factors of DR and STDR in China

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Risk Factors of Diabetic Retinopathy and Sight Threatened Diabetic Retinopathy:A Cross-sectional Studyin 13473 Patients with Type 2 Diabetes Mellitus in Mainland China

Abstract:

Objective: To explore the risk factors of diabetic retinopathy (DR) and sight threatened diabetic retinopathy (STDR) among Chinese patients with diabetes.

Design, setting and participants: A cross-sectional investigation was performed in eight screening clinics in six provinces across mainland China. Information of risk factors was recorded in screening clinics, and in these risk factors, sex, age, diagnosis age, diabetes duration, SBP, DBP, FBG, HbA1c were recorded in each clinic while others were partially collected. Relationship between risk factors and DR, risk factors and STDR were explored in both eight factors mentioned above and all factors.

Main outcomes and measures: Risk factors of DR and STDR, and a nomogram of the results.

Results: Younger age, longer diabetes duration, higher SBP, higher FBG, and higher HbA1c were independent risk factors for both DR and STDR in eight-factor analyses. In all-factor analysis, younger age, longer diabetes duration, higher SBP, oral medicine, and insulin use were independent risk factors for both DR and STDR, while higher PBG, HbA1c, triglyceride and LDL were independent risk factors only for DR, and higher FBG only for STDR.

Conclusions: In this cross-sectional investigation, several risk factors were found for

DR and STDR. What's worth to mention is that FBG, PBG and HbA1c were all risk factors for DR or STDR, which implied that a stricter blood glucose control for clinical practice was required.

Key words: diabetic retinopathy, risk factor, glucose, WHR, BMI

Strength and limitations of this study

- This is a cross-sectional population-based (13473 subjects) investigation of the risk factors of diabetic retinopathy
- The study was performed in eight hospitals from 6 different provinces in mainland China, and participants were from hospitals and communities which included rural and urban regions.
- We separately analyzed the risk factors for diabetic retinopathy (DR) and sight threatened diabetic retinopathy (STDR), which will give more implications for clinical practice.
- Owing to the multi-center design, some information was not comprehensively collected, which resulted in an imperfection in risk factor analysis.
- The sampling method of this study was not stratified, which might result in a lack of representativeness.

INTRODUCTION:

Diabetes Mellitus (DM) is a metabolic syndrome with an increasing prevalence and high rate of mortality [1]. Diabetic retinopathy (DR) is a common ocular complication of DM, which is considered as one of the leading causes of vision loss and vision impairment in adults [2]. With the progression of DR, quality of life of patients is getting lower and the financial burden of society is increasing, both in DR screening and treatment [3,4].

DR has been considered to be correlated with many other diabetes-related complications, like nephropathy, peripheral neuropathy, low bone density and cardiovascular events, which impaired the quality of life and showed a high rate of mortality [5-8]. Therefore, early diagnosis and proper management of DR would be of great realistic significance.

A great deal of epidemiologic studies of DR, either cross-sectional studies [9-18] or cohort studies [19-28], were conducted worldwide, exploring the risk factors that were associated with the disease and aiming at the prevention and management of this disease. Older age, female, duration of diabetes, renal complications of diabetes, poor glycemic control, high lipid levels, hypertension were already reported as risk factors of DR or has an impact on DR progression [9-26], which was often evaluated using Treatment Diabetic Retinopathy Study (ETDRS) classification [27]. Of these reported risk factors, duration of diabetes, hyperglycemia and hypertension were considered as most important risk factors for progression of vision loss [29]. However,

DR and risk factors of DR always gained little attention, and the compliance of eye screening is often unsatisfied [30]. More studies and publicity of risk factors are required.

In China, a few DR screening studies were conducted, while most of them were only conducted in a limited area [21,25,28]. Therefore, a cross-sectional investigation in 6 provinces (including Northern and Southern part of China) was conducted, and the prevalence of DR and basic epidemiological characteristics has been reported in former published article [31]. In this study, we aimed to explore the risk factors associated with DR and STDR in mainland China.

METHODS

Research design

Lifeline Express Diabetic Retinopathy Screening Program was conducted nationwide, which was a cross-sectional investigation in eight hospitals from 6 different provinces (Shandong, Henan, Inner Mongolia, Jilin, Guangxi, Guangdong Provinces). Subjects were recruited from hospitals and local communities (1/3 from hospital patients, 1/3 from city residents, and the other 1/3 from rural residents) between April 2014 and October 2015. The study protocol was approved by Peking University Third Hospital Ethics Committees and the written informed consent was obtained for each subject. The study was performed in accordance with the Declaration of Helsinki.

Subjects in hospital were diagnosed as DM by qualified physicians and transferred to eight screening clinics and subjects from community were recruited by advertisement, and medical records of DM diagnosis were required when they visited the screening

clinics. Of all the screening clinics, 3 of which were in the south and the other 5 were in the north of China. All subjects received a digital, colorful and non-stereoscopic retinography, which was taken by a non-mydriatic auto fundus camera. The photograph included 2 fields for each eye: one centered at the optic disc and the other centered at the macula.

DR/STDR diagnosis and grading:

DR was graded by trained and certified optometrists and ophthalmologists in Lifeline Express Diabetic Retinopathy Central Assurance Centre. All of the graders underwent periodic tests to ensure the accuracy of grading. Retinopathy was graded according to fundus photographs of two eyes into no DR(R0) and DR(other stages), and DR was also graded as none sight-threatening diabetic retinopathy (non-STDR), sight-threatening diabetic retinopathy (STDR) according to the UK guidelines[32]. Non-STDR was recognized as R0 and R1, and STDR was identified as present if any features of maculopathy (M1), pre-proliferative DR (R2) or PDR (R3) were found. If the fundus photographs were ungradable which means missing or unable to diagnose due to variable reasons in both eyes like cataract and vitreous opacities, the patients were excluded in the risk factor analysis. If photograph of one eye was unrecognized, the final diagnosis was determined by the only remained photograph. In this condition, if the remained photograph was graded as R0, patients were excluded due to lack of evidence, if graded as R1, patients were diagnosed as DR and excluded for the STDR analysis, if graded as M1, R2 or R3, patients were diagnosed as DR and STDR.

Information collection

At the time of clinical visit, the following information was recorded including gender, age, diagnosis age, diabetes duration (calculated from age and onset age), diabetes types (evaluated by physicians in screening clinics), body mass index (BMI, calculated from measured height and weight), waist–hip ratio (WHR, calculated from measured waistline and hipline), and types of treatment. Systolic blood pressure(SBP), diastolic blood pressure (DBP), fasting blood-glucose (FBG), postprandial blood glucose 2 hours after eating 75 mg glucose (PBG) and glycosylated hemoglobin (HbA1c) was measured at the screening clinics, and blood samples after fasting for 8 hours were collected for cholesterol, triglyceride, high density lipoprotein(HDL), low density lipoprotein(LDL), blood urea nitrogen(BUN), serum creatinine(Cr) measurement. Gender, age, diagnosis age, diabetes duration, blood pressure, FBG and HbA1c were collected for each patient, while other information was limited to only part of subjects due to environment and devices.

Statistical analysis

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL) software. The independent t-test was used to compare continuous variables, and the chi-square test was used to compare discontinuous variables among groups. Due to limited numbers of type 1 and gestational diabetic patients, we only analyzed the data of type 2 diabetic patients.

We firstly conducted analysis of relationship between the risk factors and DR, which contains four major steps. In the first step, mean values and median values of the

main variables were calculated. In the second step, univariate analyses of the associations between the existence of DR and risk factors. In this step, several continuous variables, including age, diabetes duration, blood pressure (BP), BMI, WHR were also transferred into categorical variables, to explore detailed relationship with DR. Age was divided into groups with 10-year interval, and diabetes duration with 5-year interval. BP was transferred into normal BP, level 1 hypertension, level 2 hypertension, and severe hypertension [33]. BMI was divided into underweight (<18.5), normal weight (≥18.5 &<24), overweight (≥24 &<28) and obesity (≥28). WHR was divided into normal WHR (male ≤0.90 &female ≤0. 85) and abdominal obesity (male 0.90 &female ≤0. 85), and was also divided into male and female. In the third step, multicollinearity diagnosis was performed and a variance inflation factor (VIF) >10 was thought a high collinearity[34], furthermore, variables with high collinearity were evaluated and variable which was more relevant to the research purpose was remained determined by two researchers (YJR and LY). In the fourth step, binary logistic regression analyses were carried out, taking the existence of DR as the dependent variable and all risk factors, which were significantly associated with the existence of DR in the former step or considered as an important risk factor based on existed studies, as independent variables. Due to limitations of information collection, we separately analyzed the eight risk factors which was completely collected in each screening clinics (eight-factor analysis), and all risk factors (all-factor analysis), furthermore, difference between two analyses was discussed.

Then, relationship between the risk factors and STDR was also conducted in

aforementioned way. Odds ratios (ORs) and 95% confidence intervals were calculated. An α level of 0.05 was adopted as the significance level.

At last, nomograms for DR and STDR risk factors were developed, and significant risk factors in former binary logistic regression were regarded as predictors. Interpretation of the nomogram in prediction of DR has been reported in former studies[35], which including two major parts. In the first part, exact values of each predictor was vertically corresponded to a certain point (the first row of the nomogram), and the total points of each predictor are calculated. In the second part, total points will corresponded to a specific risk incidence of DR and STDR (the last row of the nomogram), which will provide some implications for clinical practice.

Results

From April 2014 to October 2015, 13473 DM patients from 6 provinces were enrolled in the study. 45.9% patients were from southern provinces (6180/13473) and 54.1% from northern provinces (7293/13473). Of all the patients, 13304 patients were type 2 diabetes, 96 were type 1 diabetes, and 73 were gestational diabetes. Patients were divided into no DR and DR, non-STDR and STDR, according to the fundus photographs grading. 571 patients were excluded from DR risk factor analysis, and 683 patients were excluded from STDR risk factor analysis due to diagnostic rules mentioned above, and finally 12733 patients were included in DR risk factor analysis and 12621 patients were included in STDR risk factor analysis (shown in Figure 1).

Firstly, analyses of DR risk factors were performed, and basic characteristics of all risk factors were shown in Table 1. The result of univariate analyses indicated that age,

diagnosis age, diabetes duration, SBP, DBP, waistline, hipline, WHR, medicine (oral medication or insulin injection), FBG, PBG, HbA1c, BUN, and LDL was statistically significantly different between groups ($p<0.05$), and no significant difference was found in gender, BMI, Cr, cholesterol, triglyceride, and HDL ($p>0.05$).

Furthermore, categorical analyses showed that patients were getting less likely to suffer from DR per 10 years after 60 years old, while no difference was found before 60. Incidence of DR increased significantly per 5-year diabetes duration, while it stopped increasing after 20 years of diabetes duration. Results of blood pressure indicated that incidence increased with the rise of level, and when it came to level 3 BP, it didn't differ from level 2. Female had a higher WHR in DR while male did not, and whether in a condition of abdominal obesity did not influence the incidence of DR. Then, multivariate analyses were performed. Multicollinearity diagnosis was performed in both eight-factor analysis and all-factor analysis. The results excluded diagnosis age (highly correlated to age and DR duration) in eight-factor analysis, and excluded diagnosis age (highly correlated to age and DR duration), waistline, hipline (both of which highly correlated to WHR) in all-factor analysis due to the high collinearity. Multiple logistic regression analyses were carried out and the results were shown together with STDR analysis. Results of eight-factor analysis (with diagnosis age excluded) showed that younger age, longer diabetes duration, higher SBP, higher FBG, and higher HbA1c were the independent risk factor for DR ($p<0.05$), and sex, DBP were not significantly associated with DR ($p>0.05$). Multiple logistic regression of all-factor analysis (with diagnosis age, waistline, hipline excluded) was also

conducted and the result showed that younger age, longer diabetes duration, higher SBP, HbA1c, PBG, oral medicine, insulin use, higher triglyceride, and higher LDL were the independent risk factors for DR ($p<0.05$), while sex, DBP, BMI, FBG, WHR, BUN, Cr, cholesterol, and HDL were not associated with DR ($p>0.05$).

After DR risk factors analyses, analyses of STDR risk factors were conducted, and characteristics of risk factors were shown in Table 2. Age, diagnosis age, diabetes duration, SBP, DBP, HbA1c, FBG, PBG, waistline, WHR, medicine, Cr, LDL showed statistically significant difference between groups ($p<0.05$), while gender, BMI, hipline, BUN, cholesterol, triglyceride, HDL were not significantly different. After multicollinearity diagnosis, diagnosis age was excluded in eight-factor analysis and diagnosis age, waistline and hipline were excluded in all-factor analysis. Results of multiple logistic regression of STDR analyses (together with DR analyses) were shown in Table 3. Results of eight-factor analysis (with diagnosis age dropped) showed that younger age, longer diabetes duration, higher SBP, DBP, FBG, and HbA1c were the independent risk factor for STDR ($p<0.05$), and sex was not significantly associated with STDR ($p>0.05$). Results of all-factor analysis indicated that younger age, longer diabetes duration, higher SBP, higher FBG, oral medicine and insulin use were regarded as independent risk factors for STDR ($p<0.05$) while other risk factors showed no significant difference ($p>0.05$).

Furthermore, we subcategorized non-STDR into no DR and DR but not STDR, and risk factors between DR but not STDR and no DR, STDR and DR but not STDR were explored. The results showed that independent risk factors for DR but not STDR

compared with no DR were exactly the same as DR/no DR. However, risk factors of STDR compared to DR but not STDR analysis showed two new independent risk factors, besides those for STDR/non-STDR, which were male sex and Cr.

Finally, we developed a nomogram to simplify the presentation and understanding of our results (Figure 2).

Discussion

According to the result of our study, we tried to find a reasonable explanation and an internal relationship between DR, STDR and risk factors.

Firstly, focusing on univariate analysis, 14 out of 20 risk factors were significantly different between no DR and DR, and 13 out of 20 factors between non-STDR and STDR. Basically, all risk factors were divided into non-modifiable and modifiable risk factors. Non-modifiable factors included gender, age, diagnosis age, and diabetes duration. In both no DR/ DR and non-STDR/STDR analysis, gender showed no significant difference, which was also reported in several previous studies [10, 12], while results of some studies were controversial [11,13]. Significantly younger age was observed in DR and STDR, and longer duration of diabetes was also found in DR and STDR. Longer duration may represent a longer time of retinal toxicity induced by high glucose, which was thought to be associated with both vascular and neural death in retina [36]. Existed studies showed an older or extreme younger age in DR patients than no DR patients [26]. In our study, older age was thought as a protective variable for DR, while it's a risk variable for STDR, especially in DM patients older than 60,which means even though older age was associated with lower incidence of DR, it's more

vision threatened. We thought that this phenomenon might be explained by the higher mortality risk in older DR populations as DR was correlated with severe general diseases[37], so this result might be related to survival bias. However, older age also implied a longer suffering of hyperglycemia, which might be more vision threatened. Furthermore, we explored the relationship between age and HbA1c, diabetes duration, therapeutic regimen, the results indicated that with age increasing, diabetes duration increased, while HbA1c and use of insulin decreased, which implied that although the duration of diabetes increased, older people had a better glucose management and required milder medicine. In this way, age was determined as a protective factor.

Modifiable risk factors included types of variables as following: index of obesity, blood pressure, medicine, blood glucose, renal function and blood lipid. Both DR and STDR showed a significantly higher WHR, blood pressure, blood glucose level, LDL and a higher incidence of insulin use than no DR and non-STDR, and BUN was only significantly higher in DR than no DR, while Cr was only significantly higher in STDR than non-STDR. WHR was thought to be associated with DM [38], and was also thought as a risk factor for severe DR in women [39]. Our study showed similar results in univariate analysis. High blood pressure indicated a significantly higher incidence of DR and STDR, while the effect did not increase after a certain level. Blood glucose and LDL were significantly higher in DR and STDR group than no DR and non-STDR group, while cholesterol level showed no significant difference, which indicated DR and STDR group had a bad management of blood glucose and LDL. BUN and Cr were both common variables that reflected renal function, and our study indicated that

DR and STDR showed a higher level of renal injury than no DR and non-STDR. Application of oral medicine or insulin was also reported as risk factors in former studies, which may be owing to the severity of disease condition [11].

Secondly, the results of multiple logistic regression analyses showed independent risk factors of DR and STDR were similar in eight-factor analysis (with diagnosis age dropped) and were kind of different in all-factor analysis (with diagnosis age, waistline, hipline dropped). In all-factor analysis, younger age, diabetes duration and SBP were independent risk factors for both DR and STDR, while PBG, HbA1c, Triglyceride and LDL were independent risk factors only for DR, and FBG only for STDR. Age, diabetes duration and SBP has been reported as independent risk factors for DR or DR progression [10,20,25], while differences on blood glucose were hard to explain. HbA1c has been reported to be an independent risk factor in development and progression of DR in former studies [18,21], while there existed little evidence on PBG in DR progression. HbA1c was long considered to represent the management condition of blood glucose, and bad glucose management contributed to the occurrence and progression of DR [9,10,11]. PBG was reported to be abnormal in 31% DM patients whose FBG was normal [40], so it was considered an important diagnostic factor for DM. PBG was more valuable in prediction of ischemic and hemorrhagic stroke, cardiovascular disease mortality, while FBG was weak in prediction [41,42]. Therefore, we thought that it was reasonable PBG was a risk factor for severe complications of DM, such as DR. Possible mechanism of PBG in progression of DR might be that PBG reflected capacity of insulin secretion, the peak of which was shown to be

delayed in type 2 DM[43]. High level of PBG indicated that insulin secretion was relatively insufficient which might result in a blood glucose fluctuation after food intake, which did more harm to targeted organs. Our study firstly found that FBG was an independent risk factor for STDR, meanwhile we also admit that OR was only 1.043 for 1 unit increase in FBG, which had limited meaning in predicting incidence of STDR. No existed studies showed that FBG was an independent risk factor for DR, which might be caused by a higher predictive value of HbA1c in these studies, and possible mechanism of FBG for STDR required further studies. LDL and triglyceride were also independent risk factors for DR, which indicated that management of blood lipids were very important for DR prevention, while it had limited meanings for STDR compared with other risk factors.

Our study also had some limitations. Firstly, due to limitations of device and screening environment, several variables were incomplete and if we meant to analyze all variables in this study, lots of data would be abandoned, and the result of multivariate regression may be influenced. Secondly, although we tried to balance the resources of patients, from north and south, from urban and rural areas, patients enrolled in final all-factor logistic regression were not fully balanced due to the exclusion of missing data. Thirdly, patients and screening clinics were not stratified sampled, and could not fully represent the patient in mainland China. Fourthly, our study design was cross-sectional, compared to cohort studies, cross-sectional studies had weaker strength of evidence, and the results should be carefully explained. More cohort studies focusing on several areas of China were required.

Conclusions

Our study demonstrated that age, diabetes duration and SBP were independent risk factors for both DR and STDR. PBG, HbA1c, Triglyceride and LDL were independent risk factors only for DR, and FBG only for STDR. This result was similar to existed studies and may provide some evidence on clinical prevention of DR and STDR, especially we firstly brought up that FBG, PBG, HbA1c were all important predictors for occurrence or progression of DR, and this required a stricter glucose control. More DR screening and information collection were required, which may decrease the incidence of DR and improve clinical results.

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with the study design, data collection and contributed to the editing of the manuscript. X.L. oversaw the study, gave advise on study design, and revised the manuscript. X.L. is the guarantor of this study and had full access to all the data in this study, and X.L. also takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends.

Figure 1 Flow diagram of the data processing.

Figure 2 Nomograms for DR (A) and STDR (B) risk factors. Risk factors were chosen based on results of logistic regression analysis. Each risk factor of the patient was assessed on basis of the nomogram and got a point by vertically corresponding to the first line Aggregated points of each risk factor corresponded to a particular occurrence probability of DR or STDR in the last line.

Table 1—Univariate analysis of DR risk factors. (N=12733)

Variable	n	No DR (n=8772)	n	DR (n=3961)	P	OR	95%CI
Male gender, n(%)	8772	3985(45.4%)	3961	1851(46.7%)	0.172		
Age, years(SD)	8770	63.0(10.3)	3959	61.0(9.8)	**<0.001**		
<30, %	11	30.6%	25	69.4%			
30-40, % (vs.<30)	143	66.8%	71	33.2%	0.757	1.128	0.526-2.423
40-50, % (vs.30-40)	733	64.2%	408	35.8%	0.469	1.121	0.823-1.527
50-60, % (vs.40-50)	2138	63.2%	1243	36.8%	0.542	1.004	0.908-1.201
60-70, % (vs.50-60)	3443	69.7%	1494	30.3%	**<0.001**	0.746	0.680-0.819
>70, % (vs.60-70)	2217	76.0%	700	24.0%	**<0.001**	0.728	0.655-0.808
Diagnosis age, years (SD)	8770	56.3 (10.2)	3959	50.8 (10.3)	**<0.001**		
Diabetes duration, years (SD)	8772	6.7 (5.9)	3961	10.2 (6.8)	**<0.001**		
<5, %	4692	80.0%	1174	20.0%			
5-10, % (vs. <5)	2314	65.7%	1208	34.3%	**<0.001**	2.086	1.898-2.293
10-15, % (vs. 5-10)	1032	57.6%	761	42.4%	**<0.001**	1.413	1.257-1.587
15-20, % (vs. 10-15)	521	48.2%	560	51.8%	**<0.001**	1.458	1.252-1.696
>20, % (vs. 15-20)	213	45.2%	258	54.8%	0.281	1.127	0.907-1.400
BMI (SD)	6000	24.7 (3.5)	2854	24.9 (3.9)	0.116		
Underweight, %	97	64.7%	53	35.3%			
Normal weight, % (vs. underweight)	3348	68.5%	1543	31.5%	0.326	0.843	0.600-1.185
Overweight, % (vs. normal weight)	2175	67.6%	1043	32.4%	0.414	1.041	0.946-1.145
Obese, % (vs. overweight)	380	63.9%	215	36.1%	0.076	1.180	0.983-1.417
SBP, mmHg (SD)	8762	133.3 (16.5)	3952	137.0(17.9)	**<0.001**		
DBP, mmHg (SD)	8762	79.6 (9.9)	3952	80.8 (10.8)	**<0.001**		
Normal BP, %	5084	72.3%	1950	27.7%			
BP level 1, % (vs. normal)	2840	66.7%	1420	33.3%	**<0.001**	1.303	1.200-1.414
BP level 2, % (vs. level 1)	665	59.3%	456	40.7%	**<0.001**	1.371	1.198-1.569
BP level 3, % (vs. level 2)	173	57.9%	126	42.1%	0.648	1.062	0.820-1.376
Waistline, cm (SD)	5719	89.3 (10.1)	2735	90.3 (10.6)	**<0.001**		
Hipline, cm (SD)	5719	96.6 (9.7)	2735	97.1 (9.5)	**0.028**		
WHR (SD)	5719	0.926 (0.074)	2735	0.930 (0.069)	**0.007**		
Abdominal obesity, n(%)		4677 (81.8%)		2267 (82.9%)	0.213	1.079	0.957-1.217
Female (SD)	3152	0.915 (0.076)	1501	0.923 (0.072)	**0.002**		
Male (SD)	2567	0.94 (0.070)	1234	0.94 (0.064)	0.674		
Medicine	5793		2797		**<0.001**		

No medicine, %	660	87.0%	99	13.0%			
Oral medicine, %	3296	73.2%	1208	26.8%	**<0.001**	5.407	4.331-6.752
(vs. no medicine)							
Insulin, %	1837	55.2%	1490	44.8%	**<0.001**	2.213	2.013-2.434
(vs. oral medicine)							
FBG, mmol/L (SD)	7547	7.8 (2.4)	3517	8.7 (3.0)	**<0.001**		
PBG, mmol/L (SD)	4780	10.7 (3.3)	2095	11.8 (3.5)	**<0.001**		
HbA1c, % (SD)	7762	7.16 (1.65)	3146	7.82 (1.90)	**<0.001**		
BUN, mmol/L (SD)	6357	5.79 (8.19)	2633	6.33 (10.51)	**0.01**		
Cr, μmol/L (SD)	6320	76.5 (112.7)	2615	78.8 (39.2)	0.328		
Cholesterol, mmol/L (SD)	6418	5.04 (2.69)	2651	5.06 (1.31)	0.752		
Triglyceride, mmol/L (SD)	6382	1.87 (1.22)	2635	1.89 (1.26)	0.456		
HDL, mmol/L (SD)	6392	1.37 (0.56)	2642	1.38 (0.57)	0.481		
LDL, mmol/L (SD)	6399	2.72 (1.00)	2643	2.83 (1.00)	**<0.001**		

Continuous variables were reported as mean value and standard deviation, and categorical variables were reported as percentage, OR and 95% CI. P<0.05 was considered statistically significant and marked in bold. n, number; OR, odd ratio; 95%CI, 95% confidence interval; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist hip ratio; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; Cr, creatinine; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2—Univariate analysis of STDR risk factors. (N=12621)

Variable	n	None-STDR (n=10875)	n	STDR (n=1746)	P	OR	95%CI
Male gender, n(%)	10875	4985 (45.8%)	1746	799 (45.8%)	0.952		
Age, years (SD)	10873	62.7 (10.2)	1745	60.4 (9.7)	**<0.001**		
<30, %	32	88.9%	4	11.1%			
30-40, % (vs.<30)	181	85.0%	32	15.0%	0.757	1.128	0.526-2.423
40-50, % (vs.30-40)	927	81.9%	205	18.1%	0.469	1.121	0.823-1.527
50-60, % (vs.40-50)	2785	82.9%	576	17.1%	0.542	1.004	0.908-1.201
60-70, % (vs.50-60)	4253	86.9%	643	13.1%	**<0.001**	0.746	0.680-0.819
>70, % (vs.60-70)	2160	88.9%	270	11.1%	**<0.001**	0.728	0.655-0.808
Diagnosis age, years (SD)	10873	55.4 (10.4)	1745	49.4 (10.4)	**<0.001**		
Diabetes duration, years (SD)	10875	7.2 (6.2)	1746	11.0 (6.8)	**<0.001**		
<5, %	4692	80.0%	1174	20.0%			
5-10, % (vs. <5)	2314	65.7%	1208	34.3%	**<0.001**	2.086	1.898-2.293
10-15, % (vs. 5-10)	1032	57.6%	761	42.4%	**<0.001**	1.413	1.257-1.587
15-20, % (vs. 10-15)	521	48.2%	560	51.8%	**<0.001**	1.458	1.252-1.696
>20, % (vs. 15-20)	213	45.2%	258	54.8%	0.281	1.127	0.907-1.400
BMI (SD)	7518	24.8 (3.6)	1256	24.8 (3.9)	0.738		
Underweight	120	81.1%	28	18.9%			
Normal weight, % (vs. underweight)	4145	85.5%	703	14.5%	0.134	0.727	0.478-1.105
Overweight, % (vs. normal weight)	2759	86.6%	428	13.4%	0.177	0.915	0.804-1.041
Obese, % (vs. overweight)	494	83.6%	97	16.4%	0.054	1.266	0.995-1.610
SBP, mmHg (SD)	10863	133.8 (16.7)	1741	138.1 (18.7)	**<0.001**		
DBP, mmHg (SD)	10863	79.8 (10.0)	1741	81.0 (11.4)	**<0.001**		
Normal BP, %	6164	88.2%	826	11.8%			
BP level 1, % (vs. normal BP)	3584	85.0%	630	15.0%	**<0.001**	1.312	1.173-1.467
BP level 2, % (vs. BP level 1)	892	80.5%	216	19.5%	**<0.001**	1.378	1.161-1.635
BP level 3, % (vs. BP level 2)	223	76.4%	69	23.6%	0.118	1.278	0.939-1.739
Waistline, cm(SD)	7176	89.4 (10.1)	1200	90.7 (10.8)	**<0.001**		
Hipline, cm(SD)	7176	96.7 (9.6)	1200	97.2 (10.1)	0.120		
WHR (SD)	7176	0.926 (0.073)	1200	0.934(0.071)	**0.001**		
Abdominal obesity,n(%)		5872(81.8%)		1004(83.7%)	0.124	1.113	0.970-1.276
Female (SD)	3947	0.92 (0.075)	666	0.93 (0.074)	**<0.001**		

Male (SD)	3229	0.94 (0.069)	534	0.94 (0.065)	0.634		
Medicine	7304		1218		**<0.001**		
No medicine, %	727	93.7%	49	6.3%			
Oral medicine, % (vs. no medicine)	4008	89.6%	465	10.4%	**<0.001**	2.908	1.982-4.267
Insulin, % (vs. oral medicine)	2569	78.0%	724	22.0%	**<0.001**	2.429	2.140-2.757
FBG, mmol/L (SD)	9451	8.0 (2.5)	1521	8.9 (3.1)	**<0.001**		
PBG, mmol/L (SD)	5964	10.9 (3.3)	886	11.9 (3.6)	**<0.001**		
HbAlc, % (SD)	9548	7.25 (1.70)	1280	8.05 (1.97)	**<0.001**		
BUN, mmol/L (SD)	7855	5.89 (9.38)	1072	6.38 (4.99)	0.092		
Cr, μmol/L (SD)	7812	76.2 (102.1)	1060	84.2 (52.3)	**0.012**		
Cholesterol, mmol/L (SD)	7927	5.05 (2.48)	1079	5.06 (1.29)	0.904		
Triglyceride, mmol/L (SD)	7884	1.87 (1.22)	1072	1.94 (1.29)	0.072		
HDL, mmol/L (SD)	7897	1.37 (0.56)	1074	1.38 (0.54)	0.755		
LDL, mmol/L (SD)	7907	2.74 (0.99)	1072	2.82 (1.06)	**0.015**		

Table 3 —Logistic regression of DR and STDR risk factors. (Both in eight-factor analysis and all-factor analysis.)

Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
	DR risk factors analysis						STDR risk factors analysis					
	eight-factor analysis (N=9367)			all-factor analysis (N=4623)			eight-factor analysis (N=9303)			all-factor analysis (N=4597)		
Sex (women vs men)	1.026	0.932-1.130	0.169	1.052	0.913-1.213	0.489	0.979	0.855-1.120	0.753	1.176	0.960-1.442	0.118
Age	0.966	0.961-0.971	**<0.001**	0.968	0.961-0.976	**<0.001**	0.961	0.954-0.968	**<0.001**	0.961	0.950-0.972	**<0.001**
Diabetes duration	1.102	1.093-1.111	**<0.001**	1.071	1.059-1.084	**<0.001**	1.102	1.091-1.113	**<0.001**	1.077	1.061-1.094	**<0.001**
SBP	1.015	1.011-1.018	**<0.001**	1.016	1.010-1.021	**<0.001**	1.017	1.011-1.021	**<0.001**	1.017	1.010-1.024	**<0.001**
DBP	0.995	0.989-1.001	0.083	0.994	0.986-1.002	0.152	0.987	0.980-0.995	**0.002**	0.990	0.979-1.002	0.095
FBG	1.040	1.019-1.062	**<0.001**	1.008	0.972-1.046	0.666	1.043	1.016-1.071	**0.002**	1.076	1.028-1.127	**0.002**
HbA1c	1.164	1.128-1.201	**<0.001**	1.102	1.051-1.156	**<0.001**	1.168	1.172-1.250	**<0.001**	1.060	0.994-1.130	0.077
PBG				1.039	1.014-1.065	**0.003**				1.013	0.979-1.048	0.473
BMI				0.991	0.972-1.012	0.406				0.976	0.948-1.005	0.109
WHR				1.527	0.591-3.947	0.382				3.314	0.927-11.842	0.065
Medicine												
Oral vs. no medicine				2.158	1.517-3.069	**<0.001**				3.737	1.721-8.113	**0.001**
Insulin vs. no medicine				3.535	2.455-5.089	**<0.001**				6.856	3.141-14.966	**<0.001**
BUN				1.004	0.997-1.011	0.238				1.002	0.994-1.010	0.598
Cr				1.000	1.000-1.001	0.745				1.000	1.000-1.001	0.121
Cholesterol				0.999	0.955-1.044	0.948				0.995	0.924-1.071	0.890
Triglyceride				0.924	0.873-0.979	**0.007**				0.950	0.878-1.028	0.200

HDL	1.030	0.901-1.176	0.668	0.970	0.789-1.193	0.776
LDL	1.099	1.017-1.187	**0.017**	1.093	0.978-1.221	0.118

P<0.05 was considered statistically significant and marked in bold.

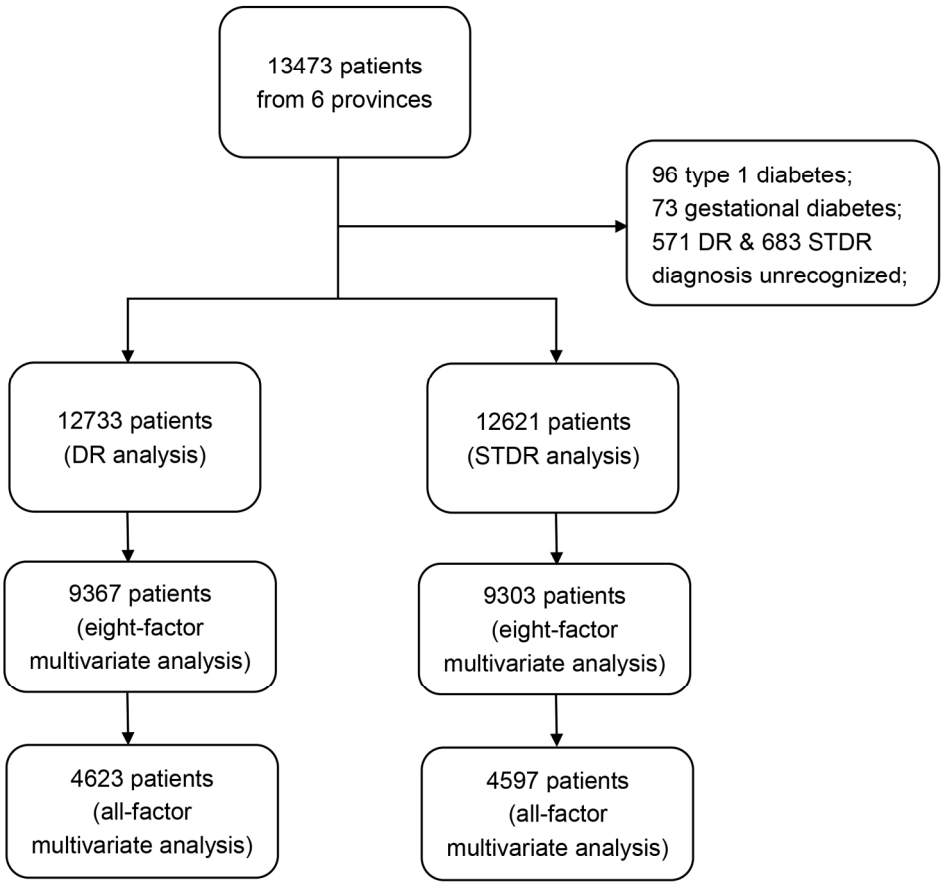

Figure 1. Flow diagram of the data processing.

163x151mm (300 x 300 DPI)

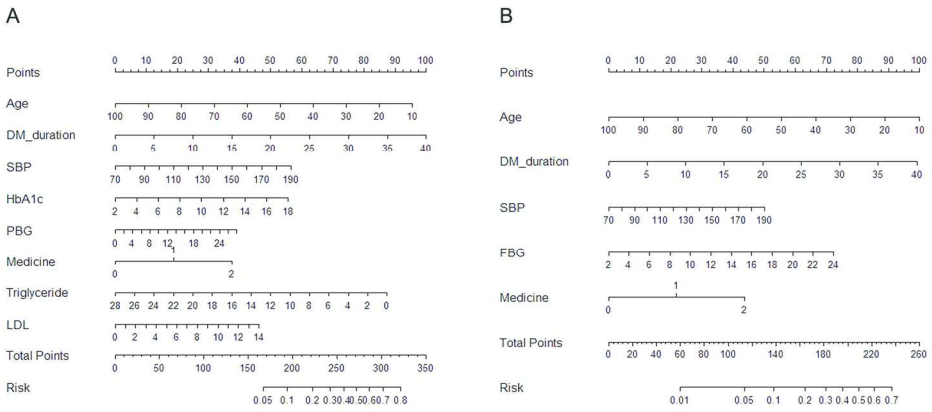

Figure 2 Nomograms for DR (A) and STDR (B) risk factors.
Risk factors were chosen based on results of logistic regression analysis. Each risk factor of the patient was assessed on basis of the nomogram and got a point by vertically corresponding to the first line Aggregated points of each risk factor corresponded to a particular occurrence probability of DR or STDR in the last line.

172x85mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	25-26
		(b) Indicate number of participants with missing data for each variable of interest	25-26
Outcome data	15*	Report numbers of outcome events or summary measures	25-26
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25-26
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk Factors of Diabetic Retinopathy and Sight-threatening Diabetic Retinopathy: A Cross-sectional Study of 13473 Patients with Type 2 Diabetes Mellitus in Mainland China.

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Title: Risk Factors of Diabetic Retinopathy and Sight-threatening Diabetic Retinopathy: A Cross-sectional Study of 13473 Patients with Type 2 Diabetes Mellitus in Mainland China.

Running title: Risk factors of DR and STDR in China

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Risk Factors of Diabetic Retinopathy and Sight-threatening Diabetic Retinopathy: A Cross-sectional Study of 13473 Patients with Type 2 Diabetes Mellitus in Mainland China

Abstract:

Objective: To explore the risk factors of diabetic retinopathy (DR) and sight-threatening diabetic retinopathy (STDR) among Chinese patients with diabetes.

Design, setting and participants: A cross-sectional investigation was performed in eight screening clinics in six provinces across mainland China. Information about the risk factors was recorded in screening clinics. Some risk factors (sex, age, diagnosis age, diabetes duration, SBP, DBP, FBG, HbA1c) were recorded in all eight clinics, while others were collected only in a subset of the clinics. The relationships between the risk factors and DR and between the risk factors and STDR were explored for the eight factors mentioned above and for all factors studied.

Main outcomes and measures: Risk factors of DR and STDR were assessed, and a nomogram of the results was produced.

Results: Younger age, longer diabetes duration, higher SBP, higher FBG, and higher HbA1c were found to be independent risk factors for both DR and STDR in the eight-factor analyses. In the all-factor analysis, younger age, longer diabetes duration, higher SBP, oral medicine use, and insulin use were independent risk factors for both DR and STDR; higher PBG, HbA1c, triglyceride and LDL were independent risk factors for DR only, and higher FBG was a risk factor for STDR only.

Conclusions: In this cross-sectional investigation, several risk factors were found for

DR and STDR. Notably, FBG, PBG and HbA1c were all risk factors for DR or STDR, suggesting that stricter blood glucose control in clinical practice is required.

Key words: diabetic retinopathy, risk factors, glucose, WHR, BMI

Strengths and limitations of this study

- This is a cross-sectional population-based (13473 subjects) investigation of the risk factors for diabetic retinopathy
- The study was performed in eight hospitals from 6 different provinces in mainland China, and participants were from hospitals and communities that included rural and urban regions.
- We separately analysed the risk factors for diabetic retinopathy (DR) and sight-threatening diabetic retinopathy (STDR), both of which have implications for clinical practice.
- Owing to the multi-centre design, some information was not comprehensively collected, which resulted in an imperfect risk factor analysis.
- The sampling method of this study was not stratified, which might result in a lack of representativeness.

INTRODUCTION:

Diabetes Mellitus (DM) is a metabolic syndrome with an increasing prevalence and high mortality rate[1]. Diabetic retinopathy (DR) is a common ocular complication of DM and is considered to be one of the leading causes of vision loss and vision impairment in adults [2]. With the progression of DR, the quality of life of patients decreases, and the financial burden on society increases, both in the DR screening and treatment groups [3,4].

DR has been considered to be correlated with many other diabetes-related complications, such as nephropathy, peripheral neuropathy, low bone density and cardiovascular events, all of which lower the quality of life and produce a high rate of mortality [5-8]. Therefore, early diagnosis and proper management of DR would be of great significance.

Many epidemiologic studies on DR, either cross-sectional studies [9-18] or cohort studies [19-28], have been conducted worldwide, exploring the risk factors that were associated with the disease and aiming at the prevention and management of this disease. Older female patients with a longer disease duration were known to be at greater risk for DR and DR progression. Furthermore, having renal complications of diabetes, poor glycaemic control, high lipid levels, or hypertension have also already been reported to be risk factors of DR, with an impact on DR progression [9-26]. These factors have been evaluated using the Treatment of Diabetic Retinopathy Study (ETDRS) classification [27]. Of these reported risk factors, the duration of diabetes,

hyperglycaemia and hypertension were considered to be the most important risk factors for progression of vision loss [29]. However, DR and the risk factors of DR have typically gained little attention, and the compliance with eye screenings is often poor[30]. More studies and an improved awareness of the risk factors are therefore required.

In China, a few DR screening studies have been conducted, but most have been completed only in a limited area [21,25,28]. Therefore, a cross-sectional investigation in 6 provinces (including the northern and southern parts of China) was conducted. The prevalence of DR and its basic epidemiological characteristics have been reported in a previously published article [31]. In this study, we sought to explore the risk factors associated with DR and STDR in mainland China.

METHODS

Research design

The Lifeline Express Diabetic Retinopathy Screening Program was conducted nationwide, and it involved a cross-sectional investigation in eight hospitals from 6 different provinces (Shandong, Henan, Inner Mongolia, Jilin, Guangxi, Guangdong Provinces). Subjects were recruited from hospitals and local communities (1/3 from hospital patients, 1/3 from city residents, and the other 1/3 from rural residents) between April 2014 and October 2015. The study protocol was approved by the Peking University Third Hospital Ethics Committee, and written informed consent was obtained for each subject. The study was performed in accordance with the Declaration of Helsinki.

In the hospital, subjects were diagnosed with DM by qualified physicians and

transferred to eight screening clinics. In the community, subjects were recruited by advertisement, and medical records of a DM diagnosis were required when they visited the screening clinics. Of all the screening clinics, 3 were in the south and 5 were in the north of China. All subjects received a digital, colourful and non-stereoscopic retinography, which was taken by a non-mydriatic auto fundus camera. The photograph included 2 fields for each eye: one centred at the optic disc and the other centred at the macula.

DR/STDR diagnosis and grading:

DR was graded by trained and certified optometrists and ophthalmologists at the Lifeline Express Diabetic Retinopathy Central Assurance Centre. All of the graders underwent periodic tests to ensure the accuracy of their grading. Retinopathy was graded according to fundus photographs of two eyes into no DR(R0) and DR (other stages), and DR was also graded as none sight-threatening diabetic retinopathy (non-STDR) or sight-threatening diabetic retinopathy (STDR) according to the UK guidelines[32]. Non-STDR was recognized as R0 and R1, while STDR was identified as present if any features of maculopathy (M1), pre-proliferative DR (R2) or PDR (R3) were found. If the fundus photographs were ungradable because of missing data or non-diagnostic images due to cataracts or vitreous opacities, the patients were excluded from the risk factor analysis. If the photograph of one eye was unrecognized, the final diagnosis was determined by the only remaining photograph. In this condition, if the remaining photograph was graded R0, patients were excluded because of a lack of evidence. If the remaining photograph was graded R1, patients were diagnosed as

DR and excluded from the STDR analysis, while if it was graded as M1, R2 or R3, patients were diagnosed as DR and STDR.

Information collection

At the time of the clinical visit, the gender, age, diagnosis age, diabetes duration (calculated from the age and onset age), diabetes type (as evaluated by physicians in screening clinics), body mass index (BMI, calculated from the measured height and weight), waist–hip ratio (WHR, calculated from the measured waistline and hipline), and type of treatment were recorded. Systolic blood pressure(SBP), diastolic blood pressure (DBP), fasting blood-glucose (FBG), postprandial blood glucose 2 hours after eating 75 mg glucose (PBG) and glycosylated haemoglobin (HbA1c) were measured at the screening clinics, and blood samples after fasting for 8 hours were collected for cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL), blood urea nitrogen (BUN), and serum creatinine (Cr) measurements. Gender, age, diagnosis age, diabetes duration, blood pressure, FBG and HbA1c were collected for each patient, while other information was limited to only part of the subjects because of the environment and devices.

Statistical analysis

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL). The independent t-test was used to compare continuous variables, and the chi-square test was used to compare discontinuous variables among the groups. Owing to the limited number of type 1 and gestational diabetic patients, we analysed

the data from the type 2 diabetic patients only.

We first conducted a four-step analysis of the relationship between the risk factors and DR. In the first step, the mean values and the median values of the main variables were calculated. In the second step, univariate analyses of the associations between the existence of DR and the risk factors were completed. In this step, several continuous variables, including age, diabetes duration, blood pressure (BP), BMI, and WHR were also transferred into categorical variables, to explore their detailed relationship with DR. Age was divided into groups with 10-year intervals, and diabetes duration was divided into groups with 5-year intervals. BP values were catalogues as normal BP, level 1 hypertension, level 2 hypertension, and severe hypertension [33]. BMI was divided into underweight (<18.5), normal weight (≥18.5 &<24), overweight (≥24 &<28) and obese (≥28) categories. WHR was divided into normal WHR (male ≤0.90 &female ≤0. 85) and abdominal obesity (male 0.90 &female ≤0. 85) and was also divided into male and female groups. In the third step, multicollinearity diagnosis was performed, and a variance inflation factor (VIF) >10 was thought to have a high collinearity[34]. Furthermore, variables with high a collinearity were evaluated, and the variable that was most relevant to the research purpose was determined by two researchers (YJR and LY). In the fourth step, binary logistic regression analyses were carried out, taking the existence of DR as the dependent variable and all risk factors, which were significantly associated with the existence of DR in the former step or considered to be important risk factors based on existing studies, as independent variables. Owing to limitations in the information collection, we separately analysed

the eight risk factors that were completely collected in each screening clinic (eight-factor analysis), and all risk factors (all-factor analysis); furthermore, the differences between the two analyses were discussed.

Then, the relationship between the risk factors and STDR was also conducted in the aforementioned way. Odds ratios (ORs) and 95% confidence intervals were calculated. An α level of 0.05 was adopted as the significance level.

At last, nomograms for DR and STDR risk factors were developed, and significant risk factors in former binary logistic regression were regarded as predictors. Interpretation of the nomogram in the prediction of DR has been reported in former studies[35], which included two major parts. In the first part, the exact values of each predictor were vertically linked to a certain point (the first row of the nomogram), and the total points of each predictor were calculated. In the second part, the total points were linked to a specific risk incidence of DR and STDR (the last row of the nomogram), which has implications for clinical practice.

Results

From April 2014 to October 2015, 13473 DM patients from 6 provinces were enrolled in the study. 45.9% patients were from the southern provinces (6180/13473) and 54.1% were from the northern provinces (7293/13473). Of all the patients, 13304 patients were diagnosed with type 2 diabetes, 96 were diagnosed with type 1 diabetes, and 73 were diagnosed with gestational diabetes. Patients were divided into a no DR and a DR group and a non-STDR and a STDR group, according to the fundus photograph grading. 571 patients were excluded from the DR risk factor analysis, and 683

patients were excluded from the STDR risk factor analysis because of the diagnostic rules mentioned above. Finally, 12733 patients were included in the DR risk factor analysis and 12621 patients were included in the STDR risk factor analysis (shown in Figure 1).

First, analyses of the DR risk factors were performed, and the basic characteristics of all risk factors are shown in Table 1. The results of the univariate analyses indicated that the age, diagnosis age, diabetes duration, SBP, DBP, waistline, hipline, WHR, medicine type (oral medication or insulin injection), FBG, PBG, HbA1c, BUN, and LDL were statistically significantly different between the groups ($p<0.05$), and no significant difference was found in the gender, BMI, Cr, cholesterol, triglyceride, and HDL ($p>0.05$).

Furthermore, our categorical analyses showed that patients were getting less likely to suffer from DR every 10 years after 60 years of age, while no difference was found before age 60. The incidence of DR increased significantly for every 5 years of diabetes duration but stopped increasing after 20 years of diabetes duration. The results of the blood pressure analysis indicated that diabetes incidence increased with increases in the blood pressure, although diabetes incidence did not differ between level 3 BP and level 2 BP. Females had a higher WHR in DR, while males did not, and the condition of abdominal obesity did not influence the incidence of DR.

Then, multivariate analyses were performed. Multicollinearity diagnosis was performed in both the eight-factor analysis and all-factor analysis. The results excluded the diagnosis age (highly correlated to the age and DR duration) in the

eight-factor analysis and excluded the diagnosis age (highly correlated to age and DR duration), waistline, and hipline (both of which were highly correlated to WHR) in the all-factor analysis because of the high collinearity. Multiple logistic regression analyses were carried out, and the results are shown with the STDR analysis. The results of eight-factor analysis (with the diagnosis age excluded) showed that younger age, longer diabetes duration, higher SBP, higher FBG, and higher HbA1c were independent risk factors for DR ($p<0.05$), and sex and DBP were not significantly associated with DR ($p>0.05$). A multiple logistic regression of the all-factor analysis (with diagnosis age, waistline, and hipline excluded) was also conducted, and the results showed that younger age, longer diabetes duration, higher SBP, HbA1c, PBG, oral medicine, insulin use, higher triglyceride, and higher LDL were the independent risk factors for DR ($p<0.05$), while sex, DBP, BMI, FBG, WHR, BUN, Cr, cholesterol, and HDL were not associated with DR ($p>0.05$).

After the DR risk factors analyses, analyses of the STDR risk factors were conducted, and characteristics of the risk factors are shown in Table 2. Age, diagnosis age, diabetes duration, SBP, DBP, HbA1c, FBG, PBG, waistline, WHR, medicine, Cr, and LDL showed statistically significant differences between groups ($p<0.05$), while gender, BMI, hipline, BUN, cholesterol, triglyceride, and HDL were not significantly different. After a multicollinearity diagnosis, the diagnosis age was excluded in the eight-factor analysis. The diagnosis age, waistline and hipline were excluded in the all-factor analysis. The results of multiple logistic regressions of STDR analyses (together with DR analyses) are shown in Table 3. The results of the eight-factor

analysis (with the diagnosis age dropped) showed that younger age, longer diabetes duration, higher SBP, DBP, FBG, and HbA1c were independent risk factors for STDR ($p<0.05$), and sex was not significantly associated with STDR ($p>0.05$). The results of the all-factor analysis indicated that a younger age, longer diabetes duration, higher SBP, higher FBG, oral medicine use and insulin use were regarded as independent risk factors for STDR ($p<0.05$), while other risk factors showed no significant differences ($p>0.05$).

Furthermore, we subcategorized the non-STDR group into the non-DR and DR but not STDR groups, and the risk factors between the DR but not STDR group and the non-DR, STDR or DR group. The results showed that independent risk factors for DR but not STDR compared with non-DR were exactly the same as for DR/no DR. However, the risk factors of the STDR compared to DR but not STDR analysis showed two new independent risk factors in addition to those for STDR/non-STDR, which were male sex and Cr.

Finally, we developed a nomogram to simplify the presentation and understanding of our results (Figure 2).

Discussion

Based on the results of our study, we tried to find a reasonable explanation and an internal relationship between DR, STDR and risk factors.

First, focusing on the univariate analysis, 14 out of 20 risk factors were found to be significantly different between the non-DR and DR groups, and 13 out of 20 factors were found to be different between the non-STDR and STDR groups. Basically, all

risk factors were divided into non-modifiable and modifiable risk factors. Non-modifiable factors included gender, age, diagnosis age, and diabetes duration. In both the non-DR/ DR and the non-STDR/STDR analyses, gender showed no significant differences. This was also reported in several previous studies [10, 12], while the results of some studies remained controversial [11,13]. Significantly younger age was observed in the DR and STDR groups, and a longer duration of diabetes was also found in the DR and STDR groups. Longer duration may represent a longer period of retinal toxicity induced by high glucose levels, which is believed to be associated with both vascular and neural death in the retina[36]. The existing studies show an older or much younger age in the DR patients than in the non-DR patients [26]. In our study, an older age seemed to be a protective variable for DR but was instead found to be a variable for STDR, especially in DM patients older than 60. This means that even though older age was associated with a lower incidence of DR, it is associated with a greater threat to vision. We thought that this phenomenon might be explained by the higher mortality risk in older DR populations. However, as DR was correlated with severe general diseases[37], this result might be related to survival bias. However, older age also implied a longer suffering of hyperglycaemia, which might be more vision threatening. Furthermore, we explored the relationship between age and HbA1c, diabetes duration, and the therapeutic regimen. The results indicated that with increasing age, the diabetes duration increased, while the HbA1c and use of insulin decreased. This implied that although the duration of diabetes increased, older people had a better glucose management and required milder medicine. In this way, age was

determined to be a protective factor.

Modifiable risk factors included the obesity index, blood pressure, medicine, blood glucose, renal function and blood lipid levels. Both DR and STDR showed a significantly higher WHR, blood pressure, blood glucose level, LDL and a higher incidence of insulin use than the non-DR and non-STDR groups. BUN was only significantly higher in the DR group than the non-DR group, meanwhile Cr was only significantly higher in the STDR than in the non-STDR group. WHR was thought to be associated with DM [38] and was also thought to be a risk factor for severe DR in women[39]. Our study showed similar results in the univariate analysis. High blood pressure indicated a significantly higher incidence of DR and STDR, while the effects did not increase after a certain level. Blood glucose and LDL were significantly higher in the DR and STDR groups than in the non-DR and non-STDR groups, while the cholesterol level showed no significant difference, indicating that the DR and STDR groups had poor management of blood glucose and LDL. BUN and Cr were both common variables that reflected renal function, and our study indicated that DR and STDR showed a higher level of renal injury than the non-DR and non-STDR groups. The application of oral medicine or insulin was also reported to be a risk factor in the former studies, perhaps because of the severity of the disease condition [11].

Second, the results of multiple logistic regression analyses showed that independent risk factors of DR and STDR were similar in the eight-factor analysis (with the diagnosis age excluded) and were different in the all-factor analysis (with diagnosis age, waistline, and hipline excluded). In the all-factor analysis, younger age, diabetes

duration and SBP were found to be independent risk factors for both DR and STDR, while PBG, HbA1c, Triglyceride and LDL were found to be independent risk factors for DR only, and FBG was found to be an independent risk factor for STDR only. Age, diabetes duration and SBP were reported to be independent risk factors for DR or DR progression [10,20,25], while differences in the blood glucose were harder to explain. HbA1c has been reported to be an independent risk factor in the development and progression of DR in earlier studies [18,21], but there is little evidence on the role of PBG in DR progression. HbA1c has long been considered to represent the management condition of blood glucose, and bad glucose management is known to contribute to the occurrence and progression of DR [9,10,11]. PBG was reported to be abnormal in 31% of DM patients whose FBG was normal [40], so it was considered to be an important diagnostic factor for DM. PBG was shown to be more valuable in the prediction of ischaemic and haemorrhagic stroke and cardiovascular disease mortality, while FBG showed only weak predictive power [41,42]. Therefore, we thought that it was reasonable that PBG was a risk factor for severe complications of DM, such as DR. One possible mechanism of PBG in the progression of DR might be that PBG reflects the capacity of insulin secretion, the peak of which was shown to be delayed in type 2 DM[43]. High levels of PBG indicate that insulin secretion is relatively insufficient, which might result in a blood glucose fluctuation after food intake and subsequent harm to the targeted organs. Our study first found that FBG was an independent risk factor for STDR, although we note that the OR was only 1.043 for a 1 unit increase in FBG and thus has a limited power to predict the incidence of STDR. No existing studies previously

showed that FBG was an independent risk factor for DR, which might be caused by a higher predictive value of HbA1c in these studies. Determining a possible mechanism of FBG for STDR required further studies. LDL and triglyceride levels were also independent risk factors for DR, which indicated that the management of blood lipids is very important for DR prevention but was of limited relevance for STDR compared with the other risk factors.

This study explored the risk factors of DR and STDR, which provided some insights for the DR progression in Chinese population, and our findings could be applied nationwide for further DR management. Our study also had some limitations. First, owing to the limitations of the device and screening environment, several variables were incomplete. If we meant to analyse all variables in this study, considerable data would be abandoned, and the results of multivariate regression might be influenced. Second, although we tried to balance patients from north and south and from urban and rural areas, the patients enrolled in the final all-factor logistic regression were not fully balanced because of the exclusion of missing data. Third, patients and screening clinics were not collected via stratified sampling and therefore were not fully representative of patients in mainland China. Fourth, our study design was cross-sectional. Compared to cohort studies, cross-sectional studies provide weaker evidence, and the results must be carefully explained. Fifth, the risk factors explored in this study had been reported in previous studies, and further studies should thus include more risk factors. More cohort studies focusing on several areas of China will therefore be required to expand on these results.

Conclusions

Our study demonstrated that age, diabetes duration and SBP were independent risk factors for both DR and STDR. PBG, HbA1c, Triglyceride and LDL were independent risk factors for DR only, and FBG was an independent risk factor for STDR only. These results are similar to the results of existing studies and may provide some evidence for the clinical prevention of DR and STDR, especially as FBG, PBG, and HbA1c were all important predictors for the occurrence or progression of DR, requiring stricter glucose control. More DR screening and information collection are required, which may decrease the incidence of DR and improve clinical results.

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oversaw the study, gave advice on the study design, and revised the manuscript. X.L. was the guarantor of this study and had full access to all the data in this study. X.L. also takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends.

Figure 1 Flow diagram of the data processing.

Figure 2 Nomograms for DR (A) and STDR (B) risk factors. Risk factors were chosen based on results of logistic regression analysis. Each risk factor of the patient was assessed on basis of the nomogram and got a point by vertically corresponding to the first line Aggregated points of each risk factor corresponded to a particular occurrence probability of DR or STDR in the last line.

Table 1—Univariate analysis of DR risk factors. (N=12733)

Variable	n	No DR (n=8772)	n	DR (n=3961)	P	OR	95%CI
Male gender, n(%)	8772	3985(45.4%)	3961	1851(46.7%)	0.172		
Age, years(SD)	8770	63.0(10.3)	3959	61.0(9.8)	**<0.001**		
<30, %	11	30.6%	25	69.4%			
30-40, % (vs.<30)	143	66.8%	71	33.2%	0.757	1.128	0.526-2.423
40-50, % (vs.30-40)	733	64.2%	408	35.8%	0.469	1.121	0.823-1.527
50-60, % (vs.40-50)	2138	63.2%	1243	36.8%	0.542	1.004	0.908-1.201
60-70, % (vs.50-60)	3443	69.7%	1494	30.3%	**<0.001**	0.746	0.680-0.819
>70, % (vs.60-70)	2217	76.0%	700	24.0%	**<0.001**	0.728	0.655-0.808
Diagnosis age, years (SD)	8770	56.3 (10.2)	3959	50.8 (10.3)	**<0.001**		
Diabetes duration, years (SD)	8772	6.7 (5.9)	3961	10.2 (6.8)	**<0.001**		
<5, %	4692	80.0%	1174	20.0%			
5-10, % (vs. <5)	2314	65.7%	1208	34.3%	**<0.001**	2.086	1.898-2.293
10-15, % (vs. 5-10)	1032	57.6%	761	42.4%	**<0.001**	1.413	1.257-1.587
15-20, % (vs. 10-15)	521	48.2%	560	51.8%	**<0.001**	1.458	1.252-1.696
>20, % (vs. 15-20)	213	45.2%	258	54.8%	0.281	1.127	0.907-1.400
BMI (SD)	6000	24.7 (3.5)	2854	24.9 (3.9)	0.116		
Underweight, %	97	64.7%	53	35.3%			
Normal weight, % (vs. underweight)	3348	68.5%	1543	31.5%	0.326	0.843	0.600-1.185
Overweight, % (vs. normal weight)	2175	67.6%	1043	32.4%	0.414	1.041	0.946-1.145
Obese, % (vs. overweight)	380	63.9%	215	36.1%	0.076	1.180	0.983-1.417
SBP, mmHg (SD)	8762	133.3 (16.5)	3952	137.0(17.9)	**<0.001**		
DBP, mmHg (SD)	8762	79.6 (9.9)	3952	80.8 (10.8)	**<0.001**		
Normal BP, %	5084	72.3%	1950	27.7%			
BP level 1, % (vs. normal)	2840	66.7%	1420	33.3%	**<0.001**	1.303	1.200-1.414
BP level 2, % (vs. level 1)	665	59.3%	456	40.7%	**<0.001**	1.371	1.198-1.569
BP level 3, % (vs. level 2)	173	57.9%	126	42.1%	0.648	1.062	0.820-1.376
Waistline, cm (SD)	5719	89.3 (10.1)	2735	90.3 (10.6)	**<0.001**		
Hipline, cm (SD)	5719	96.6 (9.7)	2735	97.1 (9.5)	**0.028**		
WHR (SD)	5719	0.926 (0.074)	2735	0.930 (0.069)	**0.007**		
Abdominal obesity, n(%)		4677 (81.8%)		2267 (82.9%)	0.213	1.079	0.957-1.217
Female (SD)	3152	0.915 (0.076)	1501	0.923 (0.072)	**0.002**		
Male (SD)	2567	0.94 (0.070)	1234	0.94 (0.064)	0.674		
Medicine	5793		2797		**<0.001**		

No medicine, %	660	87.0%	99	13.0%			
Oral medicine, % (vs. no medicine)	3296	73.2%	1208	26.8%	**<0.001**	5.407	4.331-6.752
Insulin, % (vs. oral medicine)	1837	55.2%	1490	44.8%	**<0.001**	2.213	2.013-2.434
FBG, mmol/L (SD)	7547	7.8 (2.4)	3517	8.7 (3.0)	**<0.001**		
PBG, mmol/L (SD)	4780	10.7 (3.3)	2095	11.8 (3.5)	**<0.001**		
HbA1c, % (SD)	7762	7.16 (1.65)	3146	7.82 (1.90)	**<0.001**		
BUN, mmol/L (SD)	6357	5.79 (8.19)	2633	6.33 (10.51)	**0.01**		
Cr, μmol/L (SD)	6320	76.5 (112.7)	2615	78.8 (39.2)	0.328		
Cholesterol, mmol/L (SD)	6418	5.04 (2.69)	2651	5.06 (1.31)	0.752		
Triglyceride, mmol/L (SD)	6382	1.87 (1.22)	2635	1.89 (1.26)	0.456		
HDL, mmol/L (SD)	6392	1.37 (0.56)	2642	1.38 (0.57)	0.481		
LDL, mmol/L (SD)	6399	2.72 (1.00)	2643	2.83 (1.00)	**<0.001**		

Continuous variables were reported as mean value and standard deviation, and categorical variables were reported as percentage, OR and 95% CI. P<0.05 was considered statistically significant and marked in bold. n, number; OR, odd ratio; 95%CI, 95% confidence interval; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist hip ratio; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; Cr, creatinine; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2—Univariate analysis of STDR risk factors. (N=12621)

Variable	n	None-STDR (n=10875)	n	STDR (n=1746)	P	OR	95%CI
Male gender, n(%)	10875	4985 (45.8%)	1746	799 (45.8%)	0.952		
Age, years (SD)	10873	62.7 (10.2)	1745	60.4 (9.7)	**<0.001**		
<30, %	32	88.9%	4	11.1%			
30-40, % (vs.<30)	181	85.0%	32	15.0%	0.757	1.128	0.526-2.423
40-50, % (vs.30-40)	927	81.9%	205	18.1%	0.469	1.121	0.823-1.527
50-60, % (vs.40-50)	2785	82.9%	576	17.1%	0.542	1.004	0.908-1.201
60-70, % (vs.50-60)	4253	86.9%	643	13.1%	**<0.001**	0.746	0.680-0.819
>70, % (vs.60-70)	2160	88.9%	270	11.1%	**<0.001**	0.728	0.655-0.808
Diagnosis age, years (SD)	10873	55.4 (10.4)	1745	49.4 (10.4)	**<0.001**		
Diabetes duration, years (SD)	10875	7.2 (6.2)	1746	11.0 (6.8)	**<0.001**		
<5, %	4692	80.0%	1174	20.0%			
5-10, % (vs. <5)	2314	65.7%	1208	34.3%	**<0.001**	2.086	1.898-2.293
10-15, % (vs. 5-10)	1032	57.6%	761	42.4%	**<0.001**	1.413	1.257-1.587
15-20, % (vs. 10-15)	521	48.2%	560	51.8%	**<0.001**	1.458	1.252-1.696
>20, % (vs. 15-20)	213	45.2%	258	54.8%	0.281	1.127	0.907-1.400
BMI (SD)	7518	24.8 (3.6)	1256	24.8 (3.9)	0.738		
Underweight	120	81.1%	28	18.9%			
Normal weight, % (vs. underweight)	4145	85.5%	703	14.5%	0.134	0.727	0.478-1.105
Overweight, % (vs. normal weight)	2759	86.6%	428	13.4%	0.177	0.915	0.804-1.041
Obese, % (vs. overweight)	494	83.6%	97	16.4%	0.054	1.266	0.995-1.610
SBP, mmHg (SD)	10863	133.8 (16.7)	1741	138.1 (18.7)	**<0.001**		
DBP, mmHg (SD)	10863	79.8 (10.0)	1741	81.0 (11.4)	**<0.001**		
Normal BP, %	6164	88.2%	826	11.8%			
BP level 1, % (vs. normal BP)	3584	85.0%	630	15.0%	**<0.001**	1.312	1.173-1.467
BP level 2, % (vs. BP level 1)	892	80.5%	216	19.5%	**<0.001**	1.378	1.161-1.635
BP level 3, % (vs. BP level 2)	223	76.4%	69	23.6%	0.118	1.278	0.939-1.739
Waistline, cm(SD)	7176	89.4 (10.1)	1200	90.7 (10.8)	**<0.001**		
Hipline, cm(SD)	7176	96.7 (9.6)	1200	97.2 (10.1)	0.120		
WHR (SD)	7176	0.926 (0.073)	1200	0.934(0.071)	**0.001**		
Abdominal obesity,n(%)		5872(81.8%)		1004(83.7%)	0.124	1.113	0.970-1.276
Female (SD)	3947	0.92 (0.075)	666	0.93 (0.074)	**<0.001**		

Male (SD)	3229	0.94 (0.069)	534	0.94 (0.065)	0.634		
Medicine	7304		1218		**<0.001**		
No medicine, %	727	93.7%	49	6.3%			
Oral medicine, % (vs. no medicine)	4008	89.6%	465	10.4%	**<0.001**	2.908	1.982-4.267
Insulin, % (vs. oral medicine)	2569	78.0%	724	22.0%	**<0.001**	2.429	2.140-2.757
FBG, mmol/L (SD)	9451	8.0 (2.5)	1521	8.9 (3.1)	**<0.001**		
PBG, mmol/L (SD)	5964	10.9 (3.3)	886	11.9 (3.6)	**<0.001**		
HbAlc, % (SD)	9548	7.25 (1.70)	1280	8.05 (1.97)	**<0.001**		
BUN, mmol/L (SD)	7855	5.89 (9.38)	1072	6.38 (4.99)	0.092		
Cr, μmol/L (SD)	7812	76.2 (102.1)	1060	84.2 (52.3)	**0.012**		
Cholesterol, mmol/L (SD)	7927	5.05 (2.48)	1079	5.06 (1.29)	0.904		
Triglyceride, mmol/L (SD)	7884	1.87 (1.22)	1072	1.94 (1.29)	0.072		
HDL, mmol/L (SD)	7897	1.37 (0.56)	1074	1.38 (0.54)	0.755		
LDL, mmol/L (SD)	7907	2.74 (0.99)	1072	2.82 (1.06)	**0.015**		

P<0.05 was considered statistically significant and marked in bold.

Table 3 —Logistic regression of DR and STDR risk factors. (Both in eight-factor analysis and all-factor analysis.)

Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
	DR risk factors analysis						STDR risk factors analysis					
	eight-factor analysis (N=9367)			all-factor analysis (N=4623)			eight-factor analysis (N=9303)			all-factor analysis (N=4597)		
Sex (women vs men)	1.026	0.932-1.130	0.169	1.052	0.913-1.213	0.489	0.979	0.855-1.120	0.753	1.176	0.960-1.442	0.118
Age	0.966	0.961-0.971	**<0.001**	0.968	0.961-0.976	**<0.001**	0.961	0.954-0.968	**<0.001**	0.961	0.950-0.972	**<0.001**
Diabetes duration	1.102	1.093-1.111	**<0.001**	1.071	1.059-1.084	**<0.001**	1.102	1.091-1.113	**<0.001**	1.077	1.061-1.094	**<0.001**
SBP	1.015	1.011-1.018	**<0.001**	1.016	1.010-1.021	**<0.001**	1.017	1.011-1.021	**<0.001**	1.017	1.010-1.024	**<0.001**
DBP	0.995	0.989-1.001	0.083	0.994	0.986-1.002	0.152	0.987	0.980-0.995	**0.002**	0.990	0.979-1.002	0.095
FBG	1.040	1.019-1.062	**<0.001**	1.008	0.972-1.046	0.666	1.043	1.016-1.071	**0.002**	1.076	1.028-1.127	**0.002**
HbA1c	1.164	1.128-1.201	**<0.001**	1.102	1.051-1.156	**<0.001**	1.168	1.172-1.250	**<0.001**	1.060	0.994-1.130	0.077
PBG				1.039	1.014-1.065	**0.003**				1.013	0.979-1.048	0.473
BMI				0.991	0.972-1.012	0.406				0.976	0.948-1.005	0.109
WHR				1.527	0.591-3.947	0.382				3.314	0.927-11.842	0.065
Medicine												
Oral vs. no medicine				2.158	1.517-3.069	**<0.001**				3.737	1.721-8.113	**0.001**
Insulin vs. no medicine				3.535	2.455-5.089	**<0.001**				6.856	3.141-14.966	**<0.001**
BUN				1.004	0.997-1.011	0.238				1.002	0.994-1.010	0.598
Cr				1.000	1.000-1.001	0.745				1.000	1.000-1.001	0.121
Cholesterol				0.999	0.955-1.044	0.948				0.995	0.924-1.071	0.890
Triglyceride				0.924	0.873-0.979	**0.007**				0.950	0.878-1.028	0.200

HDL	1.030	0.901-1.176	0.668	0.970	0.789-1.193	0.776
LDL	1.099	1.017-1.187	**0.017**	1.093	0.978-1.221	0.118

P<0.05 was considered statistically significant and marked in bold.

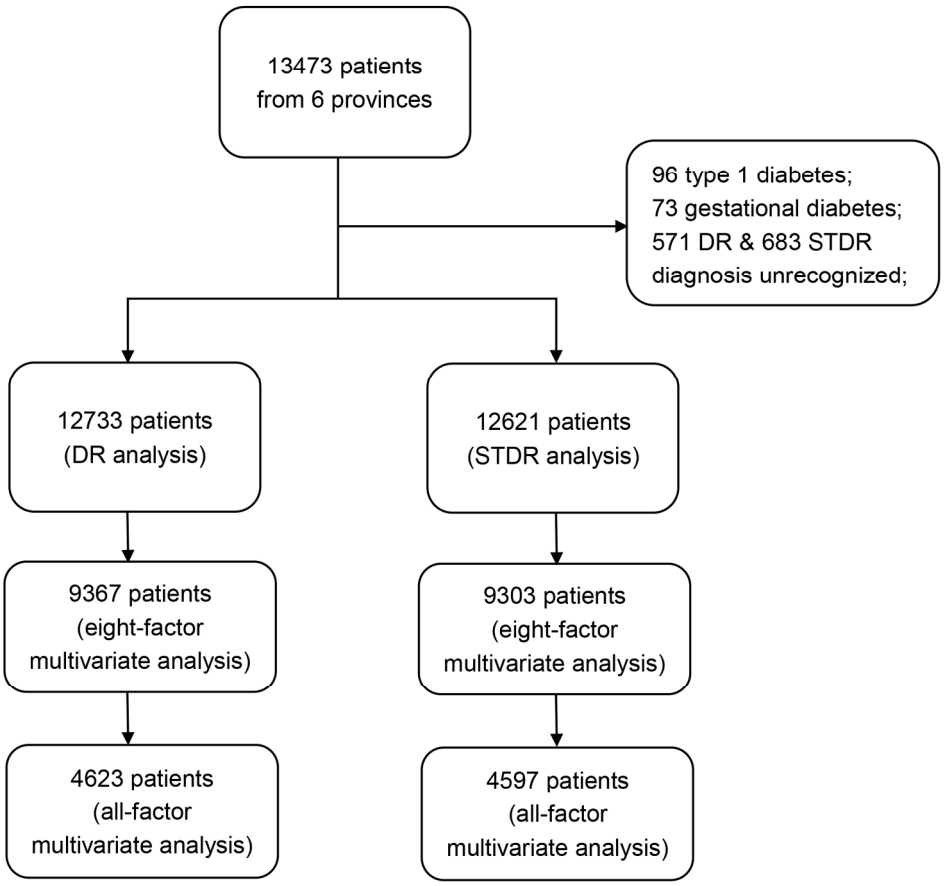

Figure 1. Flow diagram of the data processing.

163x151mm (300 x 300 DPI)

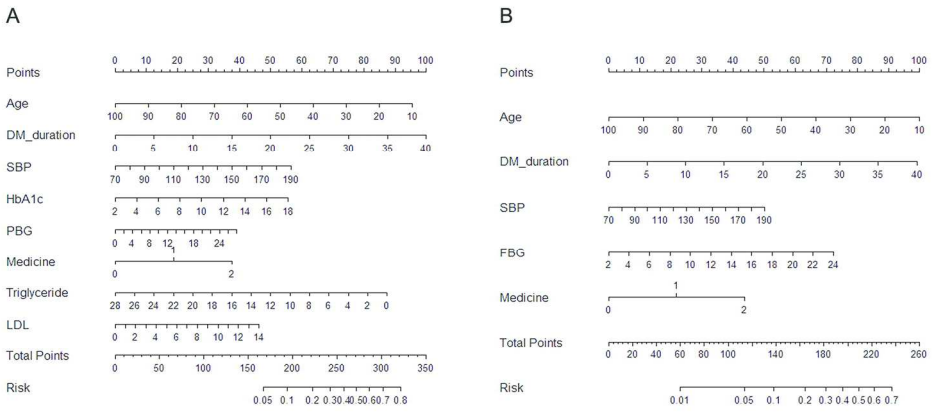

Figure 2 Nomograms for DR (A) and STDR (B) risk factors.
Risk factors were chosen based on results of logistic regression analysis. Each risk factor of the patient was assessed on basis of the nomogram and got a point by vertically corresponding to the first line Aggregated points of each risk factor corresponded to a particular occurrence probability of DR or STDR in the last line.

172x85mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9-10
		(c) Consider use of a flow diagram	Separately uploaded
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	25-26
		(b) Indicate number of participants with missing data for each variable of interest	25-26
Outcome data	15*	Report numbers of outcome events or summary measures	25-26
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25-26
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-12 (DR analysis &STDR analysis)
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.